Historic, Archive Document

Do not assume content reflects current scientific knowledge, policies, or practices.

Reserve
aTX360
.U63G72
1992

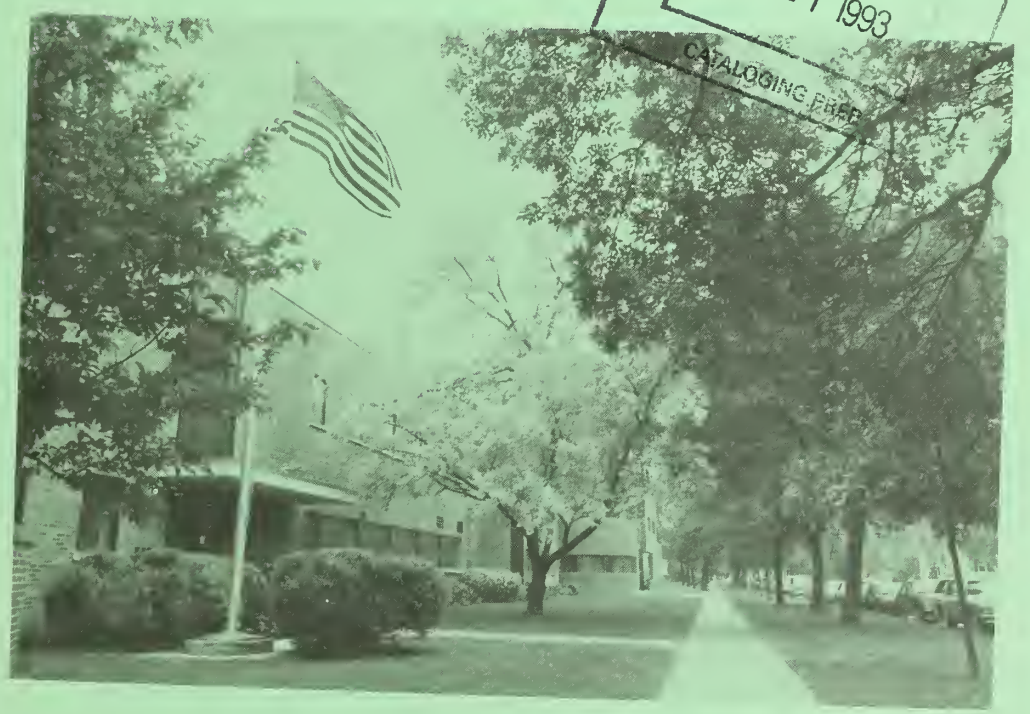
tes
nt
ure

Agricultural
Research
Service

May 1992

Grand Forks Human Nutrition Research Center

Grand Forks, North Dakota



U.S. DEPT. OF AGRICULTURE
NATIONAL AGRICULTURAL LIBRARY
APR 21 1993
CATALOGING PREP

17 AUG 1992

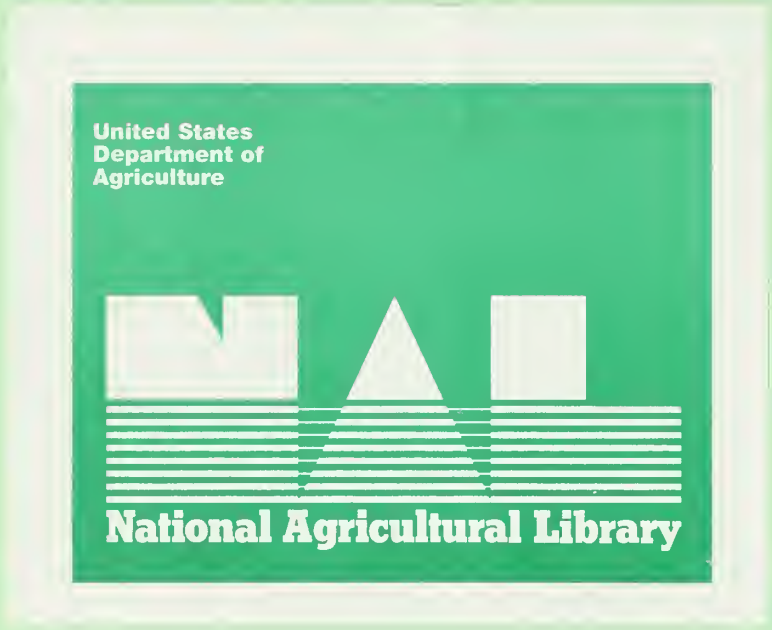

United States
Department of
Agriculture
National Agricultural Library

Table of Contents

Grand Forks Human Nutrition Research Center

Brief History

In 1963, Senator Milton Young of North Dakota submitted to Congress a report prepared by the U.S. Department of Agriculture's Agricultural Research Service (ARS) about the need for an expanded national research program in human nutrition. To accomplish an expanded program, it was proposed that three regional research laboratories be established near medical schools, one each in the North Central, Southeast and Southwest United States. The Grand Forks Human Nutrition Research Center was the only laboratory established under the original concept of the report. Planning for the facility began in 1966; construction began in 1969. The building was completed in September 1970 and dedicated with a symposium "Newer Trace Elements in Nutrition." At this time, the facility was a 1-1/2 story building of 20,000 square feet with only two finished laboratories and no animal quarters and was officially a field station of the Vitamins and Minerals Laboratory of the ARS Nutrition Division in Beltsville, MD. In 1972, the facility became the Human Nutrition Research Laboratory of the ARS North Central Region. In 1976, the laboratory began operating a clinical nutrition research program in addition to the basic animal research program. In 1977, the laboratory was designated the Grand Forks Human Nutrition Research Center (GFHNRC). The GFHNRC is one of the five human nutrition research centers operated by ARS; the others are located in Beltsville, MD; Houston, TX; Boston, MA; and San Francisco, CA.

Between the years of 1972 and 1984, the facility was expanded from 20,000 to 80,000 square feet. It now contains a vivarium with 22 separate rooms for small animals, a laboratory for each senior scientist, a 14-bed metabolic ward for long-term, live-in human volunteer studies, and a separate area for community-based human studies.

Mission

The Grand Forks Human Nutrition Research Center performs research designed to develop for humans recommended intakes of nutrients. Emphasis is on mineral requirements that will allow achievement of genetic potential and optimal function throughout the life cycle and will provide information for decisions concerning the provision of a healthful food supply to the people of the United States. The five management units that accomplish this mission are the Office of the Center Director; Location Support; Clinical Nutrition; Nutrition, Biochemistry, and Metabolism; and Nutrition, Physiology, and Behavior.

Office of the Center Director

Mission

The Office of the Center Director provides leadership in the strategic planning and coordination of research programs, funding, and staffing. It addresses safety issues and environmental concerns, assists in public relation activities, and provides library services for the Grand Forks Human Nutrition Research Center.

Center Director

Forrest H. Nielsen, Ph.D.
(701) 795-8455

Staff

Diane R. Nath
Secretary
(701) 795-8456

Beverly A. Shuler
Clerk-Typist
(701) 795-8358

Ronald G. Wien
Safety and Occupational Health Specialist
(701) 795-8487

Location Support

Mission

The mission of the Location Support Management Unit is to provide a research environment that fosters creativity, the free exchange of ideas, and interdisciplinary research related to human nutrient requirements with emphasis on minerals. Thus, the Location Support Management Unit assures provision of a physical plant and equipment that allow the achievement of high standards in research quality and quantity. This Unit also provides biostatistical support for planning experiments and evaluation of data, and administrative support for servicing personnel needs, purchasing supplies and equipment, and maintaining financial records.

Location Support Leader

Phyllis Groven
Supervisory Contract Specialist
(701) 795-8444

Staff

Deborah Meyer
Budget and Accounting Assistant
(701) 795-8354

Lauraine Troftgruben
Purchasing Agent
(701) 795-8412

Darlyne Myrvik
Purchasing Agent
(701) 795-8445

Gary Sagstuen
Procurement Clerk
(701) 795-8469 - TDD

Orris Johnson
Electronic Engineer
(701) 795-8422

Sherry Turner
Secretary/Personnel Clerk
(701) 795-8370

Lillie Magsam
Supply Clerk
(701) 795-8461

Clinical Nutrition

Mission

The Clinical Nutrition Research Unit plans, implements, and interprets research designed to produce new knowledge about human nutrient requirements, with emphasis on mineral elements. The research will identify human needs necessary for achievement of genetic potentials and optimal function throughout the life cycle. It will also provide information for decisions concerning the provision of a healthful food supply to the U.S. population.

Human volunteers are studied under controlled conditions of a metabolic research ward or as free-living individuals to determine mineral element requirements and factors that influence requirements including interactions among nutrients, and between nutrients and non-nutrients that influence nutrient bioavailability and utilization.

Research Leader

Leslie M. Klevay, M.D., S.D. in Hyg.
Supervisory Research Medcial Officer
(701) 795-8464

Mary Rydell
Secretary
(701) 795-8464

Analytical Biochemistry Laboratory

Mission

To develop methods for assessment of nutritional status with emphasis on essential trace elements and vitamins that interact with these elements. To determine effects of various dietary components on requirements and metabolism of essential trace elements.

Lead Scientist

David B. Milne, Ph.D.
Research Chemist
(701) 795-8424

Staff

Rodger Sims
Chemist
(701) 795-8425

James Botnen
Biologist
(701) 795-8404

Vacant
Postdoctoral Research Associate

Recent Research Accomplishments

Folic acid supplements of 400 μg every other day reduced urinary zinc excretion by 50 percent and increased fecal zinc losses in young men fed a diet marginal in zinc. This suggests that high dietary folic acid in relation to zinc impairs zinc absorption. Additional collaborative studies with pregnant women indicated that high blood folate and low plasma zinc were related to an increased risk of complications at delivery.

Made advances in sweat collection methods. With the advances, showed that whole body sweat losses of zinc are a significant percentage of total zinc loss. Additionally, zinc loss in sweat declines with time during zinc depletion. This suggests a homeostatic role for sweat in regulating zinc metabolism. These observations indicate that zinc lost in sweat is an important factor in determining human zinc requirements. Also showed that surface losses of copper of 1-6 percent of dietary intake may not be important for copper homeostasis.

Developed a method for the separation of platelets, mononucleated white cells, polynucleated white cells, and red blood cells on a discontinuous Percoll gradient. Apparent zinc content of the white cell fractions was dependent upon degree of separation from platelets. Subsequent studies with rats fed a severely zinc-deficient diet, and women fed a diet marginal in zinc, indicated no changes in the zinc content of blood cellular components. The findings suggest that zinc in blood cellular components is not a good indicator of zinc status. A procedure for measuring the manganese and copper content of blood cells, using graphite furnace atomic absorption spectrophotometry with Zeeman background correction, was developed. Erythrocytes accounted for about 66 percent of the total manganese in whole blood, whereas the "buffy coat" (platelets and leukocytes) accounted for about 30 percent. Because the "buffy coat" components turn over more rapidly than do erythrocytes, their manganese content may be a better indicator of manganese status.

Developed an isocratic HPLC procedure for the separation and measurement of retinol (vitamin A), α-tocopherol (vitamin E), lycopene, α-carotene, and β-carotene, extracted from plasma. The small sample size, simplicity of extraction, short run time, accuracy, and reproducibility of the method make it ideal for use in either a clinical or research setting.

Found that ethanol metabolism was significantly impaired in postmenopausal women fed a diet containing 2.6 mg Zn/day for 4 months. The impairment seemed to be corrected within 1 month upon feeding adequate zinc. Plasma zinc and key zinc-containing enzymes were maintained throughout the low zinc intake period, either by strong homeostatic mechanisms or by shifting body pools of zinc. This suggests that functional aspects of zinc biochemistry, such as ethanol metabolism, may be more sensitive indicators of zinc nutriture and stores than circulating amounts of zinc.

A metabolic study with women fed a diet containing 0.67 mg copper/day and 1.5 g ascorbic acid/day indicated that cytochrome c oxidase in platelets and white cells, and the specific enzymatic activity of ceruloplasmin, may be more sensitive indicators of copper status than plasma copper or erythrocyte superoxide dismutase. Contrary to studies with laboratory animals, ascorbic acid supplements for 6 weeks did not markedly affect commonly measured indices of copper metabolism except for the specific enzymatic activity of ceruloplasmin.

Indices of iron status were evaluated in young women as they were being depleted of iron through low iron intake and phlebotomy. The relative sensitivities of different indices for detecting iron depletion were as follows: ferritin > percent transferrin saturation > plasma iron > hemoglobin > zinc protoporphyrin and erythrocyte protoporphryn. Changes in heme synthesis evidently do not occur until iron stores are depleted and conversely, during iron repletion hematopoiesis must be satisfied before iron stores, as reflected by serum ferritin, increase. These findings indicate that one index of iron status is of limited value for detecting iron depletion. The use of two or more abnormal indices would better predict iron depletion.

Publications

David B. Milne has collaborated on nine additional publications shown in the reference lists of Dietary Interactions and Required Nutrient Intakes Laboratory; Absorption and Homeostasis of Trace Elements Laboratory; Ultratrace Elements Laboratory; Applied Physiology Laboratory; and Trace Element Nutrition, Neuropsychological Function and Behavior Research Laboratory.

1991/1992

Milne DB. Trace elements. In: *Tietz-Textbook of Clinical Chemistry*. C Burtis, E Ashwood (eds). Philadelphia: W.B. Saunders (In press).

Milne DB, Nielsen FH, Lykken GI. Effects of dietary copper and sulfur amino acids on copper homeostasis and selected indices of copper status in men. In: *Trace Elements in Man and Animals-7*. B Momčilović (ed). Zagreb, Yugloslavia: IMI, pp 5.12-5.13, 1991.

1990

Milne DB, Sims RL, Ralston NVC. Manganese content of the cellular components of blood. *Clin Chem* 36: 450-452, 1990.

Milne DB, Gallagher SK, Nielsen FH. Response of various indices of iron status to acute iron depletion produced in menstruating women by low iron intake and phlebotomy. *Clin Chem* 36: 487-491, 1990.

Milne DB. The assessment of human copper nutritional status. *AACC Nutrition Division Newsletter* 8: 1-3, 1990.

Milne DB, Johnson PE, Klevay LM, Sandstead HH. Effect of copper intake on balance, absorption, and status indices of copper in men. *Nutr Res* 10: 975-986, 1990.

Sims RL, Mullen LM, Milne DB. Application of inductively coupled plasma emission spectroscopy to multielement analysis of foodstuffs used in metabolic studies. *J Food Comp Anal* 3: 27-37, 1990.

Milne DB, Lukaski HC, Johnson PE. Effect of folic acid supplements on zinc balance and metabolism in men fed diets adequate in zinc. *J Trace Elem Exp Med* 3: 319-326, 1990.

Sandstead HH, Dintzis FR, Bogyo TP, Milne DB, Jacob RA, Klevay LM. Dietary factors that can impair calcium and zinc nutriture of the elderly. In: *Nutrition and Aging.* DM Prinsley, HH Sandstead (eds). New York: Alan R Liss, Inc, pp 241-262, 1990.

1989

Gallagher SK, Johnson LK, Milne DB. Short-term and long-term variability of indices related to nutritional status. I. Ca, Cu, Fe, Mg, and Zn. *Clin Chem* 35: 369-373, 1989.

Milne DB. Effects of folic acid supplements on zinc-65 absorption and retention. *J Trace Elem Exp Med* 2: 297-304, 1989.

Ralston NVC, Schelkoph G, Milne DB. Alterations of physiological and biochemical blood cell indices by copper deficiency. *Proc ND Acad Sci* 43: 71, 1989.

Sims RL, Ralston NVC, Milne DB. Distribution of copper and manganese in human blood and blood fractions. *Proc ND Acad Sci* 43: 84, 1989.

Metcoff J, Costiloe P, Crosby WM, Sandstead HH, Milne DB. Smoking in pregnancy: Relation of birth weight to maternal plasma carotene and cholesterol levels. *Obstet Gynecol* 74: 302-309, 1989.

Marchello MJ, Slanger WD, Milne DB, Fischer AG, Berg PT. Nutrient composition of raw and cooked Bison bison. *J Food Comp Anal* 2: 177-185, 1989.

1988

Milne DB, Klevay LM, Hunt JR. Effects of ascorbic acid supplements and a diet marginal in copper on indices of copper nutriture in women. *Nutr Res* 8: 865-873, 1988.

Justice PM, Kamath S, Langenberg PW, Sandstead HH, Milne DB, Smith GF. Micronutrients status of children with Down Syndrome: A comparative study of the effect of megadoses of vitamins with minerals or placebo. *Nutr Res* 8: 1251-1258, 1988.

Sims RL, Milne DB. Determination of manganese in whole blood and plasma using Zeeman graphite furnace AAS. *Proc ND Acad Sci* 42: 35, 1988.

Schelkoph GM, Milne DB. Microwave digestion of fecal samples for elemental analysis by inductively coupled plasma emission spectroscopy. *Proc ND Acad Sci* 42: 37, 1988.

Ralston NVC, Milne DB. Opposing effects of zinc and copper deficiencies on mean platelet volumes. *Proc ND Acad Sci* 42: 64, 1988.

Schelkoph GM, Milne DB. Wet microwave digestion of diet and fecal samples for inductively coupled plasma analysis. *Anal Chem* 60: 2060-2062, 1988.

Milne DB, Klevay LM, Hunt JR. Comparison of indices of copper status in men and women fed diets marginal in copper. In: *Trace Elements in Man and Animals-6*. LS Hurley, CL Keen, B Lönnerdal, RB Rucker (eds). New York: Plenum Press, pp 451-452, 1988.

1987

Milne DB. Assessment of zinc and copper nutritional status in man. *Nutr and the MD* 13: 1-2, 1987.

Milne DB, Canfield WK, Gallagher SK, Hunt JR, Klevay LM. Ethanol metabolism in postmenopausal women fed a diet marginal in zinc. *Am J Clin Nutr* 46: 688-693, 1987.

Sims RL, Mullen LM, Milne DB. Multielement analysis of foodstuffs using inductively coupled argon plasma. *Proc ND Acad Sci* 41: 78, 1987.

Ralston NVC, Theisen PW, Milne DB. Effects of hypertonic anticoagulants on the analytical determinations of constituents in plasma. *Proc ND Acad Sci* 41: 81, 1987.

Dietary Interactions and Required Nutrient Intakes Laboratory

Mission

To investigate human dietary requirements for trace elements, especially iron and zinc. This includes assessing the effects of marginal dietary intakes and the influence of dietary interactions on nutrient bioavailability. The nutrient content of diets is assessed by using computer-based nutrient data.

Lead Scientist

Janet R. Hunt, Ph.D., L.R.D.
(formerly Janet R. Mahalko)
Research Nutritionist
(701) 795-8328

Staff

Carol Ann Zito, M.S.
Chemist
(701) 795-8375

Laura Wilkens, B.S.
Biological Laboratory Technician
(701) 795-8375

Recent Research Accomplishments

Demonstrated that rats fed marginal dietary iron had normal blood hemoglobin, low liver iron stores, and reduced spontaneous 24-hour activity.

Demonstrated that zinc requirements increase with increased dietary protein intake and that higher protein intakes result in greater bone zinc concentration in growing rats.

Determined that approximately one-fourth of the zinc in a representative U.S. diet is absorbed.

Demonstrated that ascorbic acid supplements improve ongoing iron absorption and retention in iron-depleted women consuming a diet with poorly available iron. This was the first demonstration that ascorbic acid can improve iron retention from a whole diet rather than just single meals.

Demonstrated that iron from soybean hulls is absorbed by humans as well as iron from bakery grade ferrous sulfate. Soybean hulls could be an economical and nutritious iron source for partial enrichment of bakery products.

Using the rat model, found that zinc availability from a variety of foods correlated with the amount of protein and several amino acids, but not the amount of phytic acid in the foods.

Developed a model demonstrating that zinc absorption by rats from a test meal is proportional to the natural log of the meal zinc content and the reciprocal of the usual dietary zinc concentration; the greatest effects of zinc status on absorption are seen when low doses of zinc are used.

Publications

Janet R. Hunt has collaborated on eleven additional publications shown in the reference lists of Analytical Biochemistry Laboratory; Absorption and Homeostasis of Trace Elements Laboratory; and Ultratrace Elements Laboratory.

1991/1992

Zito CA, Hunt JR, Erjavec J, Johnson LK. The effects of deficient or marginal iron nutriture on spontaneous physical activity of rats. *Proc ND Acad Sci* 46: 74, 1992.

Hunt JR, Johnson LK. Dietary protein, as egg albumen: Effects on bone composition, zinc bioavailability, and zinc requirements of rats, assessed by a modified broken-line model. *J Nutr* 122: 161-169, 1992.

Hunt JR, Mullen LM, Lykken GI. Zinc retention by men and women consuming representative U.S. diets. In: *Trace Elements in Man and Animals-7.* B Momčilović (ed). Zagreb: IMI, pp 4.5-4.6, 1991.

Hunt JR, Lykken GI, Mullen LK. Moderate and high amounts of protein from casein enhance human absorption of zinc from whole-wheat or white rolls. *Nutr Res* 11: 413-418, 1991.

Hunt JR. Review of book. "New Techniques in Nutritional Research. Bristol-Myers Squibb/Mead Johnson Nutrition Symposia, Vol 9." Edited by RG Whitehead, A Prentice. *J Am Dietet Assoc* 91: 1350-1351, 1991.

1990

Hunt JR, Mullen LM, Lykken GI, Gallagher SK, Nielsen FH. Ascorbic acid: Effect on ongoing iron absorption and status in iron-depleted young women. *Am J Clin Nutr* 51: 649-655, 1990.

Hunt JR, Larson BJ. Meal protein and zinc levels interact to influence zinc retention by the rat. *Nutr Res* 10: 697-705, 1990.

Tekle-Wolde CA, Hunt JR. The effects of dietary protein intake on bone composition in the growing rat. *Proc ND Acad Sci* 44: 89, 1990.

Hunt JR, Mullen LM. Effect of energy intake on trace element balance. *Proc ND Acad Sci* 44: 66, 1990.

1989

Hunt JR, Johnson LK. The effect of dietary protein intake on zinc requirements and bone zinc in the growing rat. *Proc ND Acad Sci* 43: 54, 1989.

Hunt JR, Johnson PE, Swan PB. The dynamic nature of zinc availability from foods in vivo. Implications for in vitro methods. *Biol Trace Elem Res* 19: 119-127, 1989.

Hunt JR, Johnson PE, Swan PB. Effect of dietary zinc on 65-Zn absorption and turnover in rats. *Nutr Res* 9: 161-171, 1989.

Sandstead HH, Johnson L, Jacob RA, Hunt J, Henriksen LK, Dintzis FR, Lykken GI, Johnson PE, Milne DB, Lukaski HC, Klevay LM. Bioavailability of zinc from human diets. In: *Bioavailability of Micronutrients and its Human Consequences.* EG High, WL Stone (eds). Nashville: Meharry Medical College, pp 23-32, 1989.

Siu MH, Johnson LK. Computerized database management system for clinical research data using SAS/FSP, IBM DMS panels, and IBM VM-TM/SP REXX. *Proceedings of the 14th Annual SAS Users Group International Conference*, pp 1087-1092, 1989.

1988

Hunt JR. Egg white protein and zinc in a meal interact to affect zinc retention by rats. *Proc ND Acad Sci* 42: 65, 1988.

Hunt JR, Johnson PE, Swan PB. The effect of dietary Zn before and after 65-Zn administration on absorption and turnover of 65-Zn. In: *Trace Elements in Man and Animals-6*. LS Hurley, CL Keen, B Lönnerdal, RB Rucker (eds). New York: Plenum Press, pp 685-686, 1988.

Sandstead HH, Dintzis FR, Mahalko JR, Johnson LK, Bogyo TP. Effects of modest amounts of wheat bran and dietary protein on mineral metabolism of humans. In: *Trace Elements in Man and Animals-6*. LS Hurley, CL Keen, B Lönnerdal, RB Rucker (eds). New York: Plenum Press, pp 237-238, 1988.

1987

Lykken GI, Hunt JR, Nielsen EJ, Dintzis FR. Availability of soybean hull iron fed to humans in a mixed, western meal. *J Food Sci* 52: 1545-1548, 1987.

Hunt JR, Johnson PE, Swan PB. Influence of usual zinc intake and zinc in a meal on Zn-65 retention and turnover in the rat. *J Nutr* 117: 1427-1433, 1987.

Hunt JR, Johnson PE, Swan PB. The availability of zinc from foods fed to the rat. *Proc ND Acad Sci* 41: 52, 1987.

Hunt JR, Johnson PE, Swan PB. Dietary conditions influencing relative zinc availability from foods to the rat and correlations with in vitro measurements. *J Nutr* 117: 1913-1923, 1987.

Trace Elements and Cardiovascular Health Laboratory

Mission

To define the effects of copper deprivation on the cardiovascular system. The effects of copper deprivation on organs, hormones, and other metabolites that regulate cardiovascular physiology will also be studied. These studies will provide information useful in the definition of copper requirements. The effects of commonly consumed chemicals, both nutritive and non-nutritive, on copper requirements will be determined.

Lead Scientist

Leslie M. Klevay, M.D., S.D. in Hyg.
Supervisory Research Medical Officer
Research Leader
(701) 795-8464

Staff

Dale Christopherson
Chemist
(701) 795-8405

Aldrin Lafferty
Biological Laboratory Technician
(701) 795-8405

Recent Research Accomplishments

Accomplishments include the following findings:

Copper deficiency lowers the activity of enzymes that affect cholesterol metabolism. Plasma lecithin:cholesterol acyltransferase and lipoprotein lipase activities were decreased in plasma of copper-deficient rats. As low activities of these enzymes lead to higher concentrations of plasma cholesterol, these findings, which have been confirmed by others, may explain partially the hypercholesterolemia of copper deficiency.

Copper deficiency impairs glucose metabolism. Copper-deficient rats had increased glycosylated hemoglobin, an indicator of elevated plasma glucose.

Clofibrate, a lipid-lowering drug, improves copper nutriture. Clofibrate will lessen the hypercholesterolemia of copper deficiency. The effect is mediated by an increase in liver copper. This observation led to the concept of cholesterotropic and cuprotropic chemicals. Some of these--for example, aspirin, clofibrate, and sodium phytate--lower plasma cholesterol and enhance copper metabolism. Others--for example, ascorbic acid, cholesterol plus cholic acid, and zinc--raise plasma cholesterol and inhibit copper metabolism. Extra dietary copper can abolish the hypercholesterolemia caused by feeding cholesterol plus cholic acid. Since 1924, cholesterol plus cholic acid have been fed to animals to induce atherosclerosis. This procedure induces copper deficiency in rats. Cholesterol fed to rabbits without cholic acid lowers liver copper and may induce copper deficiency. This method has been used since 1913 in the induction of atherosclerosis.

Hypercholesterolemia and impaired glucose tolerance have been induced in men by feeding a low copper diet. Prolonged ingestion of a diet containing 0.8 mg of copper per day produced reversible increases in

plasma cholesterol and the height of the glucose tolerance curve. Hypercholesterolemia, glucose intolerance, and diets this low in copper are common in the U.S. population.

Copper deficiency induces atrial thrombosis. For approximately 20 years, the adverse effects of certain diets on mice were attributed to the diets being high in fat. In reality, copper had been left out of the diets. Adequate copper prevented abnormal blood clotting and abnormal cardiograms and promoted far greater longevity. This finding is similar to an earlier experiment in which a diet high in cholesterol had little effect on mice if dietary copper was adequate.

Abnormal electrocardiograms and hypercholesterolemia may be more sensitive indices of copper deficiency than anemia. Among nonanemic rats deficient in copper, abnormalities were found in the following (in order, beginning with greatest change): liver iron, heart dopamine, liver copper, plasma cholesterol, heart weight, and heart norepinephrine.

Copper deficiency produces abnormal cardiac anatomy. Mitochondrial membranes deteriorated in hearts of rats deficient in copper; debris and vacuoles were seen. The collagen fibers that hold the cardiac muscle cells together were poorly developed. The activity of choline phosphotransferase was decreased in copper deficiency; this change may partially explain some of the anatomical changes noted.

The original observation (1973) linking copper metabolism and cholesterol metabolism has been confirmed in at least 15 independent laboratories. This paper is among the more frequently quoted from the American Journal of Clinical Nutrition and was the subject of a Citation Classic essay in Current Contents.

Adult rats deficient in copper are hypertensive; this new observation has already been confirmed. The decreased blood pressure of weanling rats made deficient in copper may be caused partly by decreased activity of angiotensin converting enzyme in plasma in addition to structural defects of heart and arteries.

A new way of explaining the clinical variability of specific human illnesses has been developed. Four classes of etiologic agents--toxicity, heredity, infection, and deficiency--are known. Illnesses that are caused by cooperating members of two classes have been identified--for example, nutritional deficiency induced by a toxic agent. Three- and four-way cooperations also exist; 15 cooperative mechanisms have been identified.

Kidneys of rats fed salt and deficient in copper fail with poor perfusion of blood and very large (greater than 90 percent) decrease in aldosterone and plasma renin. Kidney failure was produced with half the salt in half the time in comparison to classical experiments.

Electroencephalograms were studied in experiments similar to those that demonstrated adverse effects of copper deficiency on electrocardiograms. Copper deficiency produced a shift to higher frequency response and a shift to more dominance of the right half of the brain.

Rats fed a diet deficient in copper were given either beer or water to drink because of extensive data demonstrating that modest consumption of beer is associated with less death from heart disease than is abstinence from alcoholic beverages. Beer drinking rats live nearly six times as long with less heart damage and higher liver copper. Results were not from either the alcohol or the copper in beer; rather, animals absorbed and retained copper better.

Slight copper deficiency was induced in young pigs by feeding their mothers high doses of zinc during pregnancy; the normal conversion of cartilage into bone during development was retarded.

Both copper deficiency and the psychological stress of intermittent, close confinement increased the blood pressure of adult rats. Rats low in copper with stress had the highest blood pressures. Copper deficiency increased the sodium in hearts.

Diets in the United States seem to be low in copper in comparison to putative requirements; 35 percent of daily diets probably contain less than 1.0 mg copper. Diets containing amounts of copper proved insufficient for volunteers in controlled experiments are readily available to the U.S. population. A unified theory is proposed that explains the high prevalence of ischemic heart disease in terms of dietary copper deficiency. Copper deficiency may induce this illness by weakening the connective tissue of arteries which are bathed in abnormal lipids and are under greater tension from high blood pressure. Arterial injury may be increased by decreased defense against oxidizing metabolites and by glycosylation of proteins. These changes result in abnormal cardiac physiology.

More than 60 similarities between animals deficient in copper and people with ischemic heart disease have been identified. The most important of these are glucose intolerance, hypercholesterolemia, abnormal electrocardiograms, hyperuricemia, hypertension, and the differential susceptibility of males and females.

Publications

Leslie M. Klevay has collaborated on thirteen additional publications shown in the reference lists of Analytical Biochemistry Laboratory; Dietary Interactions and Required Nutrient Intakes Laboratory; Applied Physiology Laboratory; Cardiovascular Physiology Laboratory; and Trace Element Nutrition, Neuropsychological Function and Behavior Research Laboratory.

1991/1992

Klevay LM. Serum copper and the risk of acute myocardial infarction. *Am J Epidemiol* (In press).

Klevay LM. Ischemic heart disease: nutrition or pharmacotherapy? In: *Trace Element Analytical Chemistry in Medicine and Biology, Vol 6.* P Brätter, P Schramel (eds). Berlin: Walter de Gruyter (In press).

Lynch SM, Klevay LM. Effects of dietary copper deficiency on plasma coagulation factor activities in male and female mice. *J Nutr Biochem* (In press).

Lykken GI, Klevay LM. Measurement of zinc and copper absorption and retention during weight loss in women. *Proc ND Acad Sci* 46: 54, 1992.

Klevay LM. The lifestyle heart trial. *Nutr Rev* 50: 29, 1992.

Klevay LM, Halas ES. The effects of dietary copper deficiency and psychological stress on blood pressure in rats. *Physiol Behavior* 49: 309-314, 1991.

Klevay LM. Can copper deficiency cause ischemic heart disease? In: *Trace Elements in Man and Animals-7.* B Momčilović (ed). Zagreb: IMI, pp 3.11-3.13, 1991.

Klevay LM. Coronary artery disease. *Wisconsin Medical Alumni Quarterly* 31: 32, 1991.

Klevay LM. Sutton's Law: rob banks because you enjoy it. *J Am Med Assoc* 266: 2376, 1991.

1990

Klevay LM. Motivation for cholesterol screening. *J Lab Clin Med* 115: 263, 1990.

Klevay LM, Moore RJ. Beer mitigates some effects of copper deficiency in rats. *Am J Clin Nutr* 51: 869-872, 1990.

Pond WG, Krook LP, Klevay LM. Bone pathology without cardiovascular lesions in pigs fed high zinc and low copper diet. *Nutr Res* 10: 871-885, 1990.

Klevay LM. Ischemic heart disease: Toward a unified theory. In: *Role of Copper in Lipid Metabolism*. KY Lei, TP Carr (eds). Boca Raton, FL: CRC Press, pp 233-267, 1990.

Klevay LM. Review of book. "Magnesium in Health and Disease." Edited by Y Itokawa and J Durlach. *J Am Dietet Assoc* 90: 1016, 1990.

Klevay LM. Some environmental aspects of ischaemic heart disease. *Environ Management and Health* 1: 9-17, 1990.

Klevay LM. Anatomy in sculpture and photography. *Sci Am* 262(2): 8, 1990.

1989

Klevay LM. Ischemic heart disease as copper deficiency. In: *Copper Bioavailability and Metabolism*. C Kies (ed). New York: Plenum, pp 197-208, 1989.

Radhakrishnamurthy B, Ruiz H, Dalferes, ER, Jr, Klevay LM, Berenson GS. Composition of proteoglycans in the aortas of copper-deficient rats. *Proc Soc Exp Biol Med* 190: 98-104, 1989.

Moore RJ, Hall CB, Carlson EC, Lukaski HC, Klevay LM. Acute renal failure and fluid retention and kidney damage in copper-deficient rats fed a high-NaCl diet. *J Lab Clin Med* 113: 516-524, 1989.

1988

Moore RJ, Klevay LM. Effect of copper deficiency on blood pressure and plasma and lung angiotensin-converting enzyme activity in rats. *Nutr Res* 8: 489-497, 1988.

Klevay LM. Dietary cholesterol lowers liver copper in rabbits. *Biol Trace Elem Res* 16: 51-57, 1988.

Klevay LM. Four ways of becoming ill. *Med Hypothesis* 27: 65-70, 1988.

Klevay LM. Cost effectiveness of antihyperlipemic therapy. *JAMA* 259: 1811, 1988.

Klevay LM. Insulin resistance in hypertension. *New Engl J Med* 318: 383, 1988.

Klevay LM. Beer increases the longevity of rats fed a diet deficient in copper. In: *Trace Elements in Man and Animals-6*. LS Hurley, CL Keen, B Lönnerdal, RB Rucker (eds). New York: Plenum Press, pp 453-454, 1988.

Klevay LM. Ambivalence on rats. *Perspect Biol Med* 31: 588, 1988.

Klevay LM. Teeny-tiny energies. *Sky and Telescope* 76: 334, 1988.

Klevay LM, Lykken GI. Reassurance regarding problems on Pennsylvania Avenue. *New Engl J Med* 316: 553-554, 1987.

Klevay LM. Scurvy as a deficiency disease. *Nutr Rev* 45: 126-127, 1987.

Klevay LM. Hypertension in rats due to copper deficiency. *Nutr Rep Int* 35: 999-1005, 1987.

Klevay LM. Cholesterol reduction: Safety, other concerns. *Ann Intern Med* 107: 421, 1987.

Klevay LM. Dietary requirements for trace elements in humans. *Proceedings of the Fourth International Workshop on Trace Element Analytical Chemistry in Medicine and Biology*. P Bratter, P Schramel (eds). 4: 43-60, 1987.

Klevay LM. Metals as nutritional factors. The IIIrd International Conference on Clinical Chemistry and Chemical Toxicology held in conjunction with the VIth International Symposium at the University of Occupational and Environmental Health. Kitakyusku, Japan, Proceedings: E Harwood Ltd., *J of the Univ of Occupational and Environmental Health 9*: Suppl, pp 59-72, 1987.

Klevay LM. Ischemic heart disease: A major obstacle to becoming old. *Clin Geriatric Med* 3: 361-372, 1987.

Klevay LM, Bistrian BR, Fleming CR, Neumann CG. Hair analysis in clinical and experimental medicine. *Am J Clin Nutr* 46: 233-236, 1987.

Klevay LM. Dietary copper: A powerful determinant of cholesterolemia. *Med Hypotheses* 24: 111-119, 1987.

Klevay LM. Dietary copper and human health. *Nutr & the MD* 13: 1-2 1987.

Klevay LM. This week's Citation Classic. (on *Am J Clin Nutr* 26: 1060, 1973). *Current Contents, Clinical Medicine* 28: 20, 1987.

Nutrition, Biochemistry, and Metabolism

Mission

The Nutrition, Biochemistry, and Metabolism Research Unit plans, implements, and interprets biochemical and metabolic studies with humans and animals that provide insights into the reasons for the essentiality of various trace elements and that show conditions under which regulation of metabolism is perturbed. This provides information about situations in which the trace element content of the diet may be of concern. Research in this unit seeks to elucidate the metabolism of the mineral elements, including the effects of mineral element deficiencies and excesses on other metabolites and the utilization of other nutrients; to define the effects of commonly ingested nutritive and non-nutritive materials on the metabolism of mineral elements; and to identify functional changes and/or adaptive mechanisms affecting responses to mineral elements. Research in this unit includes the role of copper in cell membrane function, the role of zinc in regulation of blood pressure and male reproductive function, homeostatic adjustments to changes in dietary zinc and in manganese, and the possible essentiality of certain elements such as boron and arsenic.

Acting Research Leader

Henry C. Lukaski, Ph.D.
Supervisory Research Physiologist
(701) 795-8429

Phyllis Nilsen
Secretary
(701) 795-8355

Absorption and Homeostasis of Trace Elements Laboratory

Mission

To study factors affecting the absorption, retention and utilization of trace elements from food and diets and the homeostatic regulation of trace element metabolism, and to determine how these factors affect human nutrient requirements. This work includes development of methodology for using stable isotopes in human studies and studies of the mechanisms by which trace element absorption and excretion occur. Studies in experimental animals (mainly rats) are used as preliminaries to studies in humans or to study factors that are inaccessible in humans.

Lead Scientist

Vacant

Mass Spectrometry Support Service

Richard Vanderpool, Ph.D.
Research Chemist
(701) 795-8416

Staff

John Finley, Ph.D.
Research Chemist
Postdoctoral Research Associate
(701) 795-8486

Debra Hoff
Physical Science Technician
(701) 795-8383

Eugene Korynta
Biologist
(701) 795-8415

Lorna Hammerlund
Biological Laboratory Technician
(701) 795-8486

Clariet Perreault
Biological Laboratory Technician
(701) 795-8486

Eleanor Giron
Biological Aide
(701) 795-8486

Recent Research Accomplishments

Found that Zn-65 incorporated intrinsically into beef is absorbed the same as Zn-65 added extrinsically to beef when the beef was fed as a hamburger with potatoes and a milkshake.

Found that manganese absorption in rats decreases as dietary manganese increases. The rate of manganese turnover differs depending on whether Mn-55 is administered orally or by injection.

Found that previous diet, which affected body zinc stores in rats, could affect zinc absorption and excretion; this effect occurred in addition to any effect of the current diet.

Developed an isotope dilution method for measurement of Cu absorption and endogenous excretion by rats. Used this method to measure Cu absorption and excretion in rats fed starch, glucose, fructose, and sucrose. Rats fed starch absorbed significantly more Cu than those fed the sugars.

Determined that injection of stable isotope Cu-65 into stems of wheat produces intrinsically labeled wheat which is physiologically the same as wheat with Cu incorporated through normal growth processes. Produced wheat, peanuts, and geese labeled intrinsically with Cu-65 for use in human studies.

Found that Cu-65 added intrinsically or extrinsically to wheat, goose meat, goose liver, or peanut butter is absorbed equally from a typical American meal.

Found that women fed low Mn diets (~1 mg/day) had greater menstrual losses of Mn, Fe, and total hemoglobin than women fed 5.5 mg Mn/day. Dietary supplementation with Ca (1,200 mg Ca/day) did not affect Mn absorption or turnover.

Found that intrinsic and extrinsic ^{54}Mn tracers are absorbed the same from plant foods when eaten by humans.

Found that dietary protein source does not significantly affect Mn bioavailability in rats.

Validated methodology for measuring Zn absorption and endogenous excretion in humans using stable isotopes, and developed method for measuring exchangeable Zn pools.

Found that 12-week-old infants absorb Zn and Cu more efficiently from breast milk than from infant formula, but net absorption of both Zn and Cu is greater from formula because of its higher mineral content.

Found variable boron isotope ratios in commercial produce.

Found that foliar or hydroponically grown broccoli or cabbage can be intrinsically enriched with boron-10 to levels needed for absorption studies in rats and humans.

An extrinsic/intrinsic boron study showed that fecal and urine boron isotope ratios show large changes, as measured by ICP-MS, and represents the first reported animal tracer study.

Found that meat and meat-products increase nonheme iron absorption and the factor involved appears to be saturated fats.

Found that most zinc in biliary/pancreatic secretions is associated with carboxypeptidase zymogens, active enzymes or proteolytic fragments and a small amount of zinc is associated with small peptides not associated with carboxypeptidase.

A ^{54}Mn kinetics model has been developed from rat data, and a reduced version of that model is now being used to examine the kinetics of ^{54}Mn in humans.

Found that copper absorption and rate of turnover differ between men and women and that these effects differ in young and older adults.

Found that the minimum dietary Zn requirement for young men, estimated factorially, is about 2 mg/day.

Publications

Phyllis E. Johnson has collaborated on sixteen additional publications shown in the reference lists of Analytical Biochemistry Laboratory; Dietary Interactions and Required Nutrient Intakes Laboratory; Cell Membrane Biochemistry Laboratory; Nutrition-Histopathology Laboratory; Applied Physiology Laboratory; and Trace Element Nutrition, Neuropsychological Function and Behavior Research Laboratory.

1991/1992

Johnson PE, Milne DB, Lykken GI. Effects of age and sex on copper absorption, biological half-life and status in humans. *Am J Clin Nutr* (In press).

Johnson PE, Lukaski HC, Korynta ED. The effects of stearic acid on iron utilization by the rat. *Proc Soc Exp Biol Med* (In press).

Vanderpool RA, Johnson PE. Boron isotope ratios in commercial produce and boron-10 foliar and hydroponic enriched plants. *J Agr Food Chem* (In press).

Johnson PE. Effects of copper, iron and ascorbic acid on manganese availability to rats. *Proc Soc Exp Biol Med* (In press).

Vanderpool RA, Johnson PE. Intrinsic/extrinsic boron-10 in male Long-Evans rats. *ICP Information Newsletter* 17: 213-215, 1992.

Johnson PE. Effect of food processing and preparation on mineral utilization. In: *Nutritional and Toxicological Consequences of Food Processing*. M Friedman (ed). New York: Plenum, pp 483-498, 1991.

Johnson PE, Vanderpool RA, Milne DB, Mahajan SK, Prasad AS, Mullen LK. Stable isotope studies of experimental zinc deficiency in adult men. In: *Trace Elements in Man and Animals-7*. B Momčilović (ed). Zagreb: IMI, pp 4.6-4.7, 1991.

Johnson PE, Lykken GI. Manganese and calcium absorption and balance in young women fed diets with varying amounts of manganese and calcium. *J Trace Elem Exp Med* 4: 19-35, 1991.

Johnson PE, Lykken GI, Korynta ED. Absorption and biological half-life in humans of intrinsic and extrinsic ^{54}Mn tracers from foods of plant origin. *J Nutr* 121: 711-717, 1991.

1990

Johnson PE, Nielsen FH. Copper, manganese, cobalt, and magnesium. In: *Advances in Meat Research, Volume 6: Meat and Health*. AM Pearson, TR Dutson (eds). London, England: Elsevier, pp 275-299, 1990.

Johnson PE, Gallaher DD, Lykken GI, Hunt JR. Zinc availability from beef served with various carbohydrates or beverages. *Nutr Res* 10: 155-162, 1990.

Lee DY, Korynta E, Johnson PE. Effects of sex and age on manganese metabolism in rats. *Nutr Res* 10: 1005-1014, 1990.

Johnson PE, Korynta ED. The effect of dietary protein source on manganese bioavailability to the rat. *Proc Soc Exp Biol Med* 195: 230-236, 1990.

Vanderpool RA, Johnson PE. Thermal ionization mass spectrometry of boron. *Proc ND Acad Sci* 44: 92, 1990.

Johnson PE, Lykken GI, Korynta ED. Absorption and biological half-life of Mn-54 from intrinsically and extrinsically labeled foods in humans. *Proc ND Acad Sci* 44: 68, 1990.

Vanderpool RA, Johnson PE. Natural abundance and enriched boron isotope ratios in plant material. *Proc 38th Conf on Mass Spectrom Allied Topics*, pp 79-80, 1990.

1989

Johnson PE. Factors affecting copper absorption in humans and animals. In: *Copper Bioavailability and Metabolism*. C Kies (ed). New York: Plenum, pp 71-79, 1989.

Johnson PE. What can in vitro methods tell us about mineral bioavailability? *Biol Trace Elem Res* 19: 3-10, 1989.

Lee DY, Johnson PE. ^{54}Mn absorption and excretion in rats fed soy protein and casein diets. *Proc Soc Exp Biol Med* 190: 211-216, 1989.

Johnson PE. Thermal ionization mass spectrometry of zinc in biological samples. *Proc ND Acad Sci* 43: 56, 1989.

Korynta ED, Johnson PE. The effects of animal protein on absorption and metabolism of manganese in the rat. *Proc ND Acad Sci* 43: 58, 1989.

Johnson PE. Methodology for stable isotope analysis in biological materials (A Review). *J Micronutr Anal* 6: 59-84, 1989.

Johnson PE, Canfield WK. Stable zinc and copper absorption in free-living infants fed breast milk or formula. *J Trace Elem Exp Med* 2: 285-295, 1989.

Johnson PE. Zinc absorption and excretion in humans and animals. In: *Copper and Zinc in Inflammation*. R Milanino, KD Rainsford, GP Yelo (eds). The Netherlands: Kluwer Academic Publishers, pp 103-131, 1989.

1988

Johnson PE, Evans GW, Hunt JR. The effect of picolinic acid supplementation on zinc absorption by men fed a low tryptophan diet. *Nutr Res* 8: 119-127, 1988.

Johnson PE, Lykken GI. ^{65}Cu absorption by men fed intrinsically and extrinsically labeled whole wheat bread. *J Agric Food Chem* 36: 537-540, 1988.

Johnson PE. Mean stool transit time. *Am J Clin Nutr* 48: 172, 1988.

Johnson PE, Hunt JR, Ralston NVC. The effect of past and current dietary Zn intake on Zn absorption and endogenous excretion in the rat. *J Nutr* 118: 1205-1209, 1988.

Johnson PE, Lee DY. Copper absorption and excretion measured by two methods in rats fed varying concentrations of dietary copper. *J Trace Elem Exp Med* 1: 129-141, 1988.

Johnson PE. Effect of various dietary carbohydrates on absorption and excretion of copper in the rat as measured by isotope dilution. *J Trace Elem Exp Med* 1: 143-155, 1988.

Lee DY, Johnson PE. Factors affecting absorption and excretion of ^{54}Mn in rats. *J Nutr* 118: 1509-1516, 1988.

Johnson PE, Stuart MA, Hunt JR, Mullen L, Starks TL. ^{65}Copper absorption by women fed intrinsically and extrinsically labeled goose meat, goose liver, peanut butter and sunflower butter. *J Nutr* 118: 1522-1528, 1988.

Gallaher DD, Johnson PE, Hunt JR, Lykken GI, Marchello MJ. Bioavailability in humans of zinc from beef: Intrinsic vs extrinsic labels. *Am J Clin Nutr* 48: 350-354, 1988.

Johnson PE, Stuart MA, Bowman TD. Bioavailability of copper to rats from various foodstuffs and in the presence of different carbohydrates. *Proc Soc Exp Biol Med* 187: 44-50, 1988.

1987

Johnson PE, Lukaski HC, Bowman TD. Effects of level and saturation of fat and iron level and type in the diet on iron absorption and utilization by the rat. *J Nutr* 117: 501-507, 1987.

Stuart MA, Johnson PE, Hamaker B, Kirleis A. Absorption of zinc and iron by rats fed meals containing sorghum food products. *J Cereal Sci* 6: 81-90, 1987.

Lee DY, Johnson PE. 54-Mn absorption and excretion in rats fed starch or sucrose. *Proc ND Acad Sci* 41: 53, 1987.

Hesse LJ, Johnson PE. Copper absorption and status in rats fed varying levels of dietary copper. *Proc ND Acad Sci* 41: 92, 1987.

Cell Membrane Biochemistry Laboratory

Mission

To determine the trace element requirements for maintaining normal biochemical functions of cell membranes. Emphasis on understanding the biochemical roles of copper and iron in maintaining cellular functions that are related to cell membranes. These functions include transmembrane signaling, cell proliferation, and cell differentiation.

Lead Scientist

W. Thomas Johnson, Ph.D.
Research Chemist
(701) 795-8411

Staff

Susan Sergeant, Ph.D.
Research Chemist
Postdoctoral Research Associate
(701) 795-8399

Steven N. Dufault
Biologist
(701) 795-8410

Anne C. Thomas
Biological Laboratory Technician
(701) 795-8410

Recent Research Accomplishments

Demonstrated that copper deficiency increases the amount of a 170,000 dalton protein in erythrocyte membranes. This protein is associated with the cytoskeleton and indicates that copper may be essential for maintaining normal cytoskeletal structure and function in blood cells.

Demonstrated that interactions between cytoskeletal proteins in platelets following thrombin activation are affected by copper status. When compared to rats fed adequate copper, myosin association with the cytoskeleton and actin polymerization following thrombin activation are enhanced in platelets from rats fed a copper-deficient diet.

Found that dense granule secretion from thrombin-activated platelets is increased twofold by copper deficiency in rats. This hypersecretory response is apparently related to changes in the manner by which signals are processed by the protein kinase c-dependent signaling pathway. The specific defect may involve either depressed protein kinase c activity or impaired activation of this enzyme following platelet stimulation with thrombin. Also found that the mobilization of intracellular calcium following thrombin activation and a thrombin-independent calcium transport mechanism are both impaired in platelets by copper deficiency.

Publications

W. Thomas Johnson has collaborated on one additional publication shown in the reference list of Cardiovascular Physiology Laboratory.

1991/1992

Johnson WT, Saari JT. Temporal changes in heart size, hematocrit and erythrocyte membrane protein in copper-deficient rats. *Nutr Res* 11: 1403-1414, 1991.

Johnson WT, Dufault SN. Copper deficiency alters protein kinase C mediation of thrombin-induced dense granule secretion from rat platelets. *J Nutr Biochem* 2: 663-670, 1991.

1990

Greeley S, Johnson WT, Schafer D, Johnson PE. Gestational alcoholism and fetal zinc accretion in Long-Evans rats. *J Am Coll Nutr* 9: 265-271, 1990.

Kramer TR, Johnson WT, Briske-Anderson M. Erythrocytes and latex particles enhance blastogenesis of concanavalin-A stimulated spleen lymphoid cells from copper-deficient rats. *Nutr Res* 10: 303-314, 1990.

1989

Johnson WT, Saari JT. Dietary supplementation with t-butylhydroquinone reduces cardiac hypertrophy and anemia associated with copper deficiency. *Nutr Res* 9: 1355-1362, 1989.

Johnson WT, Dufault SN. Altered cytoskeletal organization and secretory response of thrombin-activated platelets from copper-deficient rats. *J Nutr* 119: 1404-1410, 1989.

Dufault SN, Sakkinen PA, Johnson WT. Copper deficiency alters the response and cytoskeletal organization of thrombin-activated platelets. *Proc ND Acad Sci* 43: 44, 1989.

1988

Kramer TR, Johnson WT, Briske-Anderson M. Influence of iron and the sex of rats on hematological, biochemical and immunological changes during copper deficiency. *J Nutr* 118: 214-221, 1988.

1987

Johnson WT, Kramer TR. Effect of copper deficiency on erythrocyte membrane proteins of rats. *J Nutr* 117: 1085-1090, 1987.

Mayland HF, Kramer TR, Johnson WT. Trace elements in the nutrition and immunological response of grazing livestock. In: *Proceedings, Grazing Livestock Nutrition Conference*, pp 101-113, 1987.

Davis MA, Johnson WT, Briske-Anderson M, Kramer TR. Lymphoid cell functions during copper deficiency. *Nutr Res* 7: 211-222, 1987.

Canfield WK, Johnson WT. The influence of the dietary ratio of polyunsaturated to saturated fatty acids on zinc metabolism. *Nutr Res* 7: 109-119, 1987.

Nutrition-Histopathology Laboratory

Mission

To determine the essentiality, dietary requirement, interrelationships with other nutrients, and physiological function of boron, using primarily histological techniques. To determine the effects of other dietary minerals on bone, brain, and sperm morphology.

Lead Scientist

Curtiss D. Hunt, Ph.D.
Research Biologist
(701) 795-8423

Electron Microscope Support Service

Samuel M. Newman, Jr., Ph.D.
Electron Microscopist
(701) 795-8381

Staff

Jo L. Herbel
Biologist
(701) 795-8381

Joseph Idso
Biological Laboratory Technician
(701) 795-8491

Gayle H. Aasen
Biological Laboratory Technician
(701) 795-8381

Recent Research Accomplishments

Co-produced the first evidence that boron has an essential physiological role in the chick. In the chick, dietary boron affects several physiological indices including growth, tibial epiphysial growth plate calcification, and serum glucose. Previously, boron was considered essential only for plants.

Demonstrated that the effects of dietary boron on various morphological and biochemical indices are modified by the dietary concentrations of magnesium, calcium, and cholecalciferol. In the cholecalciferol-deficient chick, supplemental dietary boron enhances growth at the expense of cartilage calcification when dietary magnesium is inadequate and slows growth to the benefit of calcification when dietary magnesium is adequate.

Identified a fivefold range of boron intake that is beneficial to the cholecalciferol-deficient chick. A study with chicks indicated that optimum intake is about 1 μg B/g of dry diet. Further increases in supplemental dietary boron apparently overwhelm homeostatic controls.

Provided the first evidence that boron helps regulate energy metabolism in the rat. In the cholecalciferol-deficient rat, supplemental dietary boron markedly influenced key indicators of energy metabolism by decreasing plasma concentrations of creatine kinase, insulin, and pyruvate, and by increasing plasma concentrations of thyroxine.

Provided the first evidence that boron protects the integrity of kidney function/structure from acute phase nephrotoxin-induced damage. Rats injected 24 hours previously with streptozotocin exhibited an abnormal elevation of total 24-hour urinary albumin, potassium, and sodium; supplemental dietary boron alleviated the abnormal elevations. However, the protective influence of supplemental dietary boron was apparently overwhelmed with time; 48 hours after injection, compared to boron-deprived controls, the rats supplemented with dietary boron exhibited increased urinary excretion of those substances.

Developed a new low-temperature, wet-ashing method for use in boron analysis of biological tissues and fluids and foodstuffs. This method minimizes the loss of boron from the sample through volatilization. Volatilization is a significant problem in boron analysis methodology.

Determined that the daily intake of boron usually differs considerably between any two individuals by analyzing a variety of typical Western foods and personal care products. The concentration of boron in water varies considerably according to geographical source; at some locations the boron in drinking water and water-based beverages may account for most of the total dietary boron intake. Individual food preference greatly influences daily intake of boron; fruits, vegetables, tubers, and legumes have relatively much higher concentrations of boron than cereal grains or animal tissues and fluids. Also, boron is a significant contaminant of, or major ingredient of, many different personal care products.

Demonstrated that inadequate zinc nutriture during infancy, despite postlactational zinc repletion, induced imbalances in adult bone mineral metabolism when compared to zinc-adequate, pair-fed rat pups. At 150 days of age, zinc-deficient rat pups exhibited increased concentrations of bone phosphorus and magnesium and decreased concentrations of bone potassium.

Demonstrated that short-term zinc depletion (35 days) in humans affects several aspects of andrology, especially seminal volume. Compared to when they were consuming 10.4 mg Zn/day, volunteers consuming 1.4 mg Zn/day exhibited decreased semen volumes and serum testosterone concentrations, but no change in seminal zinc concentrations. Treatments of 1.4, 2.5, and 3.4 mg Zn/day decreased the total semen zinc loss per ejaculate. Seminal loss accounted for 9 percent of total body zinc loss when 1.4 mg zinc was consumed per day.

Publications

Curtiss D. Hunt has collaborated on three additional publications shown in the reference list of Ultratrace Elements Laboratory.

1991/1992

Hunt CD, Herbel JL. Boron affects energy metabolism in the streptozotocin-injected, vitamin D_3-deprived rat. *Mg Tr Elem Res* (In press).

Hunt CD, Herbel JL. Effects of dietary boron on calcium and mineral metabolism in the streptozotocin-injected, vitamin D_3-deprived rat. *Mg Tr Elem Res* (In press).

Hunt CD. Boron. In: *Encyclopaedia of Food Science, Food Technology and Nutrition*. R Macreae, R Robinson, M Sadler, G Fullerlove (eds). London: Academic Press Limited (In press.)

Hunt CD, Johnson PE, Herbel J, Mullen LK. The effects of dietary zinc depletion on seminal volume and zinc loss, serum testosterone concentrations and sperm morphology in young men. *Am J Clin Nutr* (In press).

Hunt CD. The research nutritionist and the market place. *Nutr Rep* (In press).

Hunt CD, Idso J. Effects of boron, training exercise and their interaction in male rats. *Proc ND Acad Sci* 46: 72, 1992.

Herbel J, Hunt CD. Dietary boron modifies the effects of thiamine nutriture in the male rat. *Proc ND Acad Sci* 46: 71, 1992.

Hunt CD, Shuler TR, Mullen LM. Concentration of boron and other elements in human foods and personal-care products. *J Am Diet Assoc* 91: 558-568, 1991.

Hunt CD, Johnson PE. The effects of dietary zinc on human sperm morphology and seminal mineral loss. In: *Trace Elements in Man and Animals-7.* B Momčilović (ed). Zagreb: IMI, pp 4.9-4.11, 1991.

Muessig KD, Hunt CD. The effects of dietary boron, vitamin D_3 and their interaction on glycolytic metabolites in chicks. *Proc ND Acad Sci* 45: 25, 1991.

1990

Hunt CD, Achen V, Johnson PE. Effects of short-term dietary zinc deficiency on sperm morphology and motility in humans. *Proc ND Acad Sci* 44: 65, 1990.

Herbel J, Hunt CD, Johnson PE. Effects of short-term dietary zinc deficiency on semen mineral concentrations in humans. *Proc ND Acad Sci* 44: 63, 1990.

Muessig KD, Hunt CD. Effects of boron, streptozotocin and their interaction on organ mineral concentrations in vitamin D_3-deficient rats. *Proc ND Acad Sci* 44: 74, 1990.

1989

Hunt CD, Shuler TR. Open-vessel, wet-ash, low-temperature digestion of biological materials for inductively coupled argon plasma spectroscopy (ICAP) analysis of boron and other elements. *J Micronutrient Anal* 6: 161-174, 1989.

Hunt CD. Dietary boron modified the effects of magnesium and molybdenum on mineral metabolism in the cholecalciferol-deficient chick. *Biol Trace Elem Res* 22: 201-220, 1989.

Hunt CD, Kalliokoski S, Herbel JL. Effects of boron, streptozotocin and their interaction on intermediate metabolism and bone turnover in rats. *Proc ND Acad Sci* 43: 53, 1989.

Achen V, Hunt CD. Use of an advanced image analysis system to determine the effects of dietary boron on bone morphology in the cholecalciferol-deficient chick. *Proc ND Acad Sci* 43: 37, 1989.

Herbel JL, Shuler TR, Ralston NVC, Hunt CD. Semi-closed, teflon tube, wet-ash digestion for the determination of boron in biological substances by inductively coupled argon plasma spectrophotometry. *Proc ND Acad Sci* 43: 52, 1989.

1988

Hunt CD, Halas ES, Eberhardt MJ. Long-term effects of lactational zinc deficiency on bone mineral composition in rats fed a commercially modified Luecke diet. *Biol Trace Elem Res* 16: 97-113, 1988.

Hunt CD, Nielsen FH. Dietary boron affects bone calcification in magnesium and cholecalciferol-deficient chicks. In: *Trace Elements in Man and Animals-6.* LC Hurley, CL Keen, B Lönnerdal, RB Rucker (eds). New York: Plenum Press, pp 275-276, 1988.

Hunt CD. Boron homeostasis in the cholecalciferol-deficient chick. *Proc ND Acad Sci* 42: 60, 1988.

1987

Hunt CD, Nielsen FH. Interactions among dietary boron, magnesium, and cholecalciferol in the chick. *Proc ND Acad Sci* 41: 50, 1987.

Peptide Hormone Metabolism and Cell Culture Laboratories

Mission

To determine the biochemical function of zinc in humans and animals. The emphasis for this research is placed on the role of zinc in metabolism and function of physiologically active peptides as acted upon by the zinc-dependent family of peptidases.

Lead Scientist

Philip G. Reeves, Ph.D.
Supervisory Research Chemist
(701) 795-8497

Staff

Mary Briske-Anderson, M.S.
Biologist
(701) 795-8402

Kerry Rossow, M.S.
Biologist
(701) 795-8496

Brenda Skinner
Biological Laboratory Technician
(Biochemistry)
(701) 795-8496

Alyssa Martinez
Biological Aide
(701) 795-8402

Recent Research Accomplishments

Our laboratory is studying the involvement of zinc (Zn) in the metabolism of certain peptide hormones. Zinc is a cofactor for many of the enzymes that either synthesize or degrade many of the active peptides. Angiotensin converting enzyme (ACE), which converts a nonactive peptide, angiotensin I, into a very potent vasoactive peptide, angiotensin II, is affected by Zn nutriture. This enzyme is important in the regulation of blood pressure in all animals, including humans. It is also important in reproduction in the male because it is found in very high concentration in the testes and sperm. We find that in the Zn-deficient rat, blood pressure is lowered and, if the deficiency is begun before puberty, the testes do not mature.

Our latest research has focused on the effect of Zn deficiency on ACE synthesis in the testes. We have isolated pure ACE from normal, mature rat testes by affinity chromatography and used it to produce high titer antibodies in rabbits. We have developed an enzyme linked immunosorbent assay (ELISA) to detect minute quantities of this protein. Using this assay, we recently found that Zn deficiency also decreases the ACE protein concentration in testes. There was a direct correlation between enzyme activity and enzyme protein concentration. The next step is to determine if Zn deficiency affects the tissue concentration of ACE mRNA.

Endothelial cells line the vascular system. They have abundant ACE, and those of the lung and kidney are thought to be involved with the renin-angiotensin-system that regulates blood pressure. We have successfully grown endothelial cells in culture and have attempted to show an effect of media Zn deficiency on ACE activity. Because it appears that endothelial cells require very little Zn in the media to grow, we turned our attention to how this cell type might handle Zn. Recently, D.J. Bobilya, a

research associate in our lab, published some elegant work describing the kinetics of Zn transport and some characteristics of the transporter. This work will further our understanding of Zn metabolism in this as well as other cell types.

Publications

Philip G. Reeves has collaborated on one additional publication shown in the reference list of Cardiovascular Physiology Laboratory.

1991/1992

Reeves PG, Rossow KL. Exposure to excessive parenteral Zn and/or cisplatin affects trace element metabolism and enzyme activities in reproductive organs and kidney of male rats. *J Nutr Biochem* (In press).

Bobilya DJ, Briske-Anderson M, Reeves PG. Zinc transport into endothelial cells is facilitated by a specific transporter. *J Cell Physiol* (In press).

Briske-Anderson M, Reeves PG. The effect of high zinc on the uptake of copper in Caco-2 cells in culture. *Proc ND Acad Sci* 46: 76, 1992.

Rossow KL, Reeves PG. The effect of zinc deficiency on angiotensin converting enzyme concentrations in rat testes: Measurement by enzyme-linked immunosorbent assay. *Proc ND Acad Sci* 46: 77, 1992.

Reeves PG, Nelson KL. Effect of zinc pretreatment on cisplatin toxicity and trace element metabolism in rats. *J Tr Elem Exp Med* 4: 89-101, 1991.

Bobilya DJ, Briske-Anderson M, Johnson LK, Reeves PG. Zinc exchange by endothelial cells in culture. *J Nutr Biochem* 2: 565-569, 1991.

Reeves PG, Nelson KL. cis-diamminedichloroplatinum treatment and trace element metabolism in rats fed different amounts of dietary zinc and copper. In: *Trace Elements in Man and Animals-7.* B Momčilović (ed). Zagreb: IMI, pp 24.8-24.9, 1991.

1990

Reeves PG. Zinc deficiency and dipeptidyl carboxypeptidase activity: Comparative effects on epididymis and testis of rats. *Biol Tr Elem Res* 24: 1-11, 1990.

Reeves PG. Effects of zinc deficiency and testosterone treatment on the activities of dipeptidyl carboxypeptidase and other enzymes in the testis of rats. *Nutr Res* 10: 859-869, 1990.

Reeves PG, Noordewier B, Saari JT. Effect of copper deficiency and cis-diamminedichloroplatinum (II) treatment on the activities of renal microvillar enzymes in rats. *J Tr Elem Electrolytes Health Dis* 4: 11-19, 1990.

Reeves PG, Saari JT. Effect of cis-diamminedichloroplatinum (II) on metallothionein induction and trace element metabolism in rats fed different amounts of dietary zinc. *J Nutr Biochem* 1: 374-381, 1990.

Bobilya DJ, Briske-Anderson M, Reeves PG. Zinc uptake by endothelial cells. *Proc ND Acad Sci* 44: 52, 1990.

1989

Reeves PG. Effect of testosterone treatment on reproductive organ growth of Zn-deficient male rats. *Proc ND Acad Sci* 43: 72, 1989.

Reeves PG. AIN-76 diet: Should we change the formulation. *J Nutr* 119: 1081-1082, 1989.

O'Dell BL, Reeves PG. Zinc status and food intake. In: *Zinc in Human Biology*. CF Mills (ed). London, United Kingdom: Springer-Verlag, pp 173-181, 1989.

1988

Reeves PG, O'Dell BL. Zinc deficiency in rats and angiotensin-converting enzyme activity: Comparative effects on lung and testis. *J Nutr* 118: 622-626, 1988.

Reeves PG. Effect of Zn deficiency on the activity of angiotensin converting enzyme in reproductive organs of testosterone-treated male rats. *Proc ND Acad Sci* 42: 66, 1988.

Reeves PG, O'Dell BL. Effect of zinc deficiency on blood pressure in rats fed normal and high levels of dietary calcium. *Nutr Res* 8: 1143-1150, 1988.

1987

O'Dell BL, Browning JD, Reeves PG. Zinc deficiency increases osmotic fragility of rat erythrocytes. *J Nutr* 117: 1883-1889, 1987.

Browning JD, Reeves PG, O'Dell BL. Zinc deficiency in rats reduces the vasodilation responses to bradykinin and prostacyclin. *J Nutr* 117: 490-495, 1987.

Briske-Anderson M, Kramer TR. The influence of zinc deficiency and bacillus calmette-guerin cell wall injection on the proliferation of concanavalin-A stimulated lymphoid cells. *Proc ND Acad Sci* 41: 51, 1987.

Ultratrace Elements Laboratory

Mission

To determine the essentiality, dietary requirement, utilization, interrelationships with other nutrients, and biochemical function of certain chemical elements, including arsenic, boron, nickel, silicon, and vanadium, found in ultratrace amounts in food.

Lead Scientist

Eric O. Uthus, Ph.D.
Research Chemist
(701) 795-8382

Co-Lead Scientist

Forrest H. Nielsen, Ph.D.
Supervisory Nutritionist
(701) 795-8456

Staff

Carol D. Seaborn, Ph.D.
Research Nutritionist
Postdoctoral Research Associate
(701) 795-8406

Rhonda A. Poellot
Biologist
(701) 795-8406

Debbie Johnson
Physical Science Technician
(701) 795-8364

Julie A. Stump
Biological Laboratory Technician
(701) 795-8406

Terrence R. Shuler
Chemist
(701) 795-8364

Thomas J. Zimmerman
Biologist
(701) 795-8359

David Allard
Physical Science Technician
(701) 795-9364

Mike Colombe
Biological Aide
(701) 795-8406

Recent Research Accomplishments

Produced the first evidence suggesting that nickel has an essential role in animals. Showed that nickel influences iron metabolism through physiologic, pharmacologic, and toxicologic mechanisms. Also showed that vitamin B_{12} and biotin status, and luxuriant amounts of an odd-chain fatty acid (margaric acid), in the diet affects the response of rats to nickel deprivation. These findings suggest that vitamin B_{12} may be necessary for the optimal expression of the biologic role of nickel, and this role affects metabolic pathways involving vitamin B_{12} and biotin. Because of this, nickel nutriture affects fat and methionine or sulfur amino acid metabolism. Thus, nickel might be of nutritional significance.

Co-produced the first evidence that boron is an essential nutrient for animals. Signs of boron deficiency were found to vary in nature and severity as diets varied in content of substances that affect macro mineral metabolism--for example, calcium, potassium, and magnesium. Findings to date indicate that boron deprivation alters the function or composition of the skeleton, kidney, and brain. Prior to these findings, boron was considered essential only for plants. The findings established boron as an element to be considered in human nutrition.

Produced the first evidence showing that boron may be nutritionally important for humans. Findings were obtained which indicated that the supplementation of a boron-low diet with an amount of boron commonly found in diets high in fruits and vegetables induces in postmenopausal women changes consistent with the prevention of calcium loss and bone demineralization. Also, boron was found to enhance and to mimic some of the effects of estrogen therapy in postmenopausal women. Boron nutriture may be an important factor in the occurrence of some of the problems associated with the postmenopausal phase of life.

Found that, in humans, boron deprivation reduces blood hemoglobin concentration, mean corpuscular hemoglobin concentration and mean corpuscular hemoglobin, and increases hematocrit, red blood cell count, and platelet count. The findings are consistent with the hypothesis that boron affects membrane function, and thus indirectly affects many variables, including those associated with erythropoiesis and hematopoiesis.

Produced the first evidence suggesting that arsenic is an essential trace element. Demonstrated that dietary methionine and arginine markedly affect the response of chicks to arsenic deprivation. Also showed that arsenic deprivation in rats and chicks is affected by dietary manipulations affecting labile methyl metabolism. Produced the first evidence that arsenic deprivation decreases the concentration of liver polyamines in rats. The findings indicate that arsenic is important physiologically as a methylated compound or is involved in labile methyl metabolism. The findings should help in defining the essential role of arsenic and in determining whether arsenic is a practical human nutrition concern.

Produced the first evidence that dietary vanadium deprivation affects thyroid function of the rats. Vanadium deprivation elevates thyroid weight and depresses the activity of thyroid peroxidase. The findings suggest that vanadium might be essential for optimal thyroid function or thyroid hormone metabolism. However, findings were obtained which indicate that vanadium does not directly affect deiodinase (extrathyroidal) enzymes. These findings also should help determine whether vanadium is a practical nutritional concern for animals including humans.

Found that both bone turnover and bone formation as indicated by acid and alkaline phosphatase in femurs are depressed in animals fed inadequate silicon. Also, calcium-45 uptake by ectopic bone in rats is decreased by silicon deprivation. Silicon apparently is necessary for normal bone metabolism.

Demonstrated that genetic factors, sex, and dietary sulfur amino acids markedly affect the nature and severity of the signs of copper deficiency in rats and humans. The findings indicate that the signs of copper deficiency in humans are not likely to be consistent and have implications for the hypothesis that copper nutriture affects cardiovascular health.

Showed for the first time that experimentally significant effects other than on urinary magnesium can be obtained by the dietary restriction of magnesium in otherwise healthy adults. Magnesium deprivation apparently adversely affects the erythrocyte membrane, changes indices associated with bone metabolism and causes heart rhythm abnormalities. Magnesium may be of more nutritional concern than currently acknowledged.

Publications

Forrest H. Nielsen has collaborated on seven additional publications shown in the reference lists of Analytical Biochemistry Laboratory; Dietary Interactions and Required Nutrient Intakes Laboratory; Absorption and Homeostasis of Trace Elements Laboratory; Nutrition-Histopathology Laboratory; and Applied Physiology Laboratory.

1991/1992

Nielsen FH. Fact and fallacies about boron. *Nutr Today* (In press).

Nielsen FH. Trace elements. Physiology of trace elements. In: *Encyclopaedia of Food Science, Food Technology and Nutrition*. London: Harcourt Brace Jovanovich (In press).

Fowle JR III, Abernathy CO, McKinney JD, Mass MJ, North DW, Uthus EO. Health effects of arsenic in drinking water. *Tr Sub Environ Health* (In press).

Uthus E, Poellot R. The effect of dietary pyridoxine on arsenic deprivation in rats. *Mg Tr Elem* (In press).

Nielsen FH, Gallagher SK, Johnson LK, Nielsen EJ. Boron enhances and mimics some effects of estrogen therapy in postmenopausal women. *Mg Tr Elem* (In press).

Nielsen FH, Shuler TR, Uthus EO. Dietary arginine and methionine effects, and their modification by dietary boron and potassium, on the mineral element composition of plasma and bone in the rat. *Mg Tr Elem* (In press).

Nielsen FH. Studies of the interaction between boron and calcium and its modification by magnesium and potassium in rats: Effects on growth, blood variables and bone mineral composition. *Biol Tr Elem Res* (In press).

Nielsen FH. Chapter 11. Boron, chromium, manganese, nickel, tin and vanadium. In: *Trace Elements in Human Nutrition*. WHO Technical Report Series, WHO/FAO/IAEA (In press).

Nielsen FH. Chromium. In: *Modern Nutrition in Health and Disease, 8th ed*. ME Shils, JA Olson, M Shike (eds). Philadelphia: Lea & Febiger (In press).

Nielsen FH. Ultratrace elements. In: *Modern Nutrition in Health and Disease, 8th ed*. ME Shils, JA Olson, M Shike (eds). Philadelphia: Lea & Febiger (In press).

Nielsen FH. Ultratrace elements of possible importance for human health: An update. In: *Essential and Toxic Trace Elements in Human Health and Disease*. AS Prasad (ed). New York: Wiley (In press).

Nielsen FH, Milne DB. High dietary fructose affects plasma cholesterol concentrations and signs of short-term copper deprivation in men. *Proc ND Acad Sci* 46: 73, 1992.

Uthus EO. The effect on arsenic deprivation in rats of diethyl maleate, an *in vivo* chemical depletor of glutathione. *Proc ND Acad Sci* 46: 70, 1992.

Poellot RA, Seaborn CD, Uthus EO. The effect of vanadium deprivation in thyroxine replete-thyroidectomized rats. *Proc ND Acad Sci* 46: 75, 1992.

Nielsen FH, Mullen LM, Nielsen EJ. Dietary boron affects blood cell counts and hemoglobin concentrations in humans. *J Tr Elem Exp Med* 4: 211-223, 1991.

Nielsen FH. Studies on the essentiality of some elements ascribed as toxic - arsenic, boron, lead, tin and vanadium. In: *Trace Elements in Man and Animals-7*. B Momčilović (ed). Zagreb: IMI, pp 35.2-35.4, 1991.

Nielsen FH, Milne DB. The effect of copper deprivation on variables associated with glucose metabolism in men. In: *Trace Elements in Man and Animals-7*. B Momčilović (ed). Zagreb: IMI, pp 3.2-3.4, 1991.

Nielsen FH. Trace elements (nutrition). In: *Encyclopedia of Human Biology, vol 7*. R Dulbecco (ed). San Diego: Academic Press, pp 603-613, 1991.

Nielsen FH. Review of book. "Lithium and Cell Physiology." Edited by RO Bach, VS Gallicchio. *The Quarterly Review of Biology* 66: 76, 1991.

Nielsen FH. Trace and ultratrace elements in health and disease. *Comprehensive Therapy* 17: 20-26, 1991.

Nielsen FH. Review of book. "Metal Ions in Biological Systems, vol 26: Compendium on Magnesium and Its Role in Biology, Nutrition, and Physiology." Edited by H Sigel, A Sigel. *J Toxicol Environ Health* 33: 249-250, 1991.

Nielsen FH. Nutritional requirements for boron, silicon, vanadium, nickel, and arsenic: Current knowledge and speculation. *FASEB J* 5: 2661-2667, 1991.

Nielsen FH. Trace and ultratrace elements in human health and disease. In: *Mineral Update '91, A Nutrition Workshop for Health Professionals*. Kansas City: Dairy Council of Greater Kansas City, pp 10-21, 1991.

Shuler TR, Nielsen FH. The modification of rat bone mineral composition by changes in dietary arginine, methionine, boron and potassium. *Proc ND Acad Sci* 45: 27, 1991.

Nielsen FH. Nutritional importance of the ultratrace elements. *The Nutrition Report* 9: 80, 84, 88, 1991.

Nielsen FH. The saga of boron in food: From a banished food preservative to a beneficial nutrient for humans. *Curr Top Plant Biochem Physiol* 10: 274-286, 1991.

1990

Nielsen FH, Uthus EO. The essentiality and metabolism of vanadium. In: *Vanadium in Biological Systems: Physiology and Biochemistry*. ND Chasteen (ed). The Netherlands: Kluwer Academic Publishers, pp 51-62, 1990.

Nielsen FH. New essential trace elements for the life sciences. *Biol Tr Elem Res* 26/27: 599-611, 1990.

Nielsen FH. New essential trace elements for the life sciences. In: *Nuclear Analytical Methods in the Life Sciences*. R Zeisler, VP Guinn (eds). Clifton: Humana Press, pp 599-611, 1990.

Nielsen FH. Ultratrace minerals - Mythical elixirs or nutrients of concern? *Contemporary Nutrition* 15: No. 7, 1990.

Uthus EO. Effects of arsenic deprivation in hamsters. *Mg Tr Elem* 9: 227-232, 1990.

Uthus EO, Nielsen FH. Effect of vanadium, iodine and their interaction on growth, blood variables, liver trace elements and thyroid status indices in rats. *Mg Tr Elem* 9: 219-226, 1990.

Nielsen FH, Milne DB, Mullen LM, Gallagher SK. Dietary sulfur amino acids and genetic make-up or interindividual variation affect the response of men to copper deprivation. *J Trace Elem Exp Med* 3: 281-296, 1990.

Nielsen FH. Studies on the relationship between boron and magnesium which possibly affects the formation and maintenance of bones. *Mg Tr Elem* 9: 61-69, 1990.

Nielsen FH. Other trace elements. In: *Present Knowledge in Nutrition, 6th ed.* ML Brown (ed). Washington, DC: International Life Sciences Institute, pp 294-307, 1990.

Nielsen FH. Ultratrace elements: An update. In: *Trace Elements in Clinical Medicine*. H Tomita (ed). Tokyo, Japan: Springer-Verlag, pp 353-360, 1990.

Nielsen FH. Diet: The neglected variable in laboratory animal care. *Lab Animal* 19: 45-46, 1990.

Brossart B, Shuler TR, Nielsen FH. Effect of silicon deficiency on the mineral composition of bone. *Proc ND Acad Sci* 44: 95, 1990.

Shuler TR, Zimmerman TJ, Nielsen FH. Copper deprivation affects the plasma amino acid profile in rats. *Proc ND Acad Sci* 44: 87, 1990.

Uthus EO, Poellot R. Effects of dietary methionine on signs of arsenic deprivation in rats. *Proc ND Acad Sci* 44: 90, 1990.

Poellot RA, Shuler TR, Uthus EO, Nielsen FH. Dietary margaric acid affects the response to nickel deprivation and the interaction between nickel and vitamin B-12 in the rat. *Proc ND Acad Sci* 44: 80, 1990.

Nielsen FH. Magnesium deprivation effects on plasma cholesterol and erythrocytes of healthy postmenopausal women. *Proc ND Acad Sci* 44: 76, 1990.

Nielsen FH, Mullen LM, Gallagher SK. Effect of boron depletion and repletion on blood indicators of calcium status in humans fed a magnesium-low diet. *J Trace Elem Exp Med* 3: 45-54, 1990.

Shuler TR, Pootrakul P, Yarnsukon P, Nielsen FH. Effect of thalassemia/hemoglobin E disease on macro, trace, and ultratrace element concentrations in human tissue. *J Trace Elem Exp Med* 3: 31-43, 1990.

Nielsen FH, Hunt JR. Trace elements emerging as important in human nutrition. In: *Proceedings of the Fourteenth National Nutrient Databank Conference*. PJ Stumbo (ed). Ithaca, NY: The CBORD Group, pp 135-143, 1990.

1989

Nielsen FH. Reference materials for neglected trace elements: Future needs. In: *Proceedings of the 14th International Congress of Nutrition, Vol II*. KW Young, LY Cha, LK Yull, JJ Soon, KS He (eds). Seoul, Korea: Ewha Womans University, pp 253-254, 1989.

Nielsen FH. Recent advances in human trace and ultratrace element nutrition. In: *Proceedings of the 14th International Congress of Nutrition, Vol I.* KW Young, LY Cha, LK Yull, JJ Soon, KS He (eds). Seoul, Korea: Ewha Womans University, pp 184-187, 1989.

Nielsen FH. Dietary boron affects variables associated with copper metabolism in humans. In: *6th International Trace Element Symposium, Vol 4: As, B, Br, Co, Cr, F, Fe, Mn, Ni, Sb, Sc, Si, Sn, and Other Ultra Trace Elements.* M Anke, W Baumann, H Braunlich, Chr Bruckner, B Groppel, M Grun (eds). Jena, DDR: Karl-Marx-Universitat, Leipzig and Friedrich-Schiller-Universitat, pp 1106-1111, 1989.

Uthus EO, Poellot R, Nielsen FH. The effect of arsenic deprivation on polyamine content and the activity of s-adenosylmethionine and ornithine decarboxylase in rat liver. In: *6th International Trace Element Symposium, Vol 4: As, B, Br, Co, Cr, F, Fe, Mn, Ni, Sb, Sc, Si, Sn, and Other Ultra Trace Elements.* M Anke, W Baumann, H Braunlich, Chr Bruckner, B Groppel, M Grun (eds). Jena, DDR: Karl-Marx-Universitat, Leipzig and Friedrich-Schiller-Universitat, pp 1013-1017, 1989.

Nielsen FH, Shuler TR. Effect of dietary sulfur amino acids on some signs of copper deficiency in rats. In: *6th International Trace Element Symposium, Vol 2: Cu, Zn and Other Trace Elements.* M Anke, W Baumann, H Braunlich, Chr Bruckner, B Groppel, M Grun (eds). Jena, DDR: Karl-Marx-Universitat, Leipzig and Friedrich-Schiller-Universitat, pp 526-533, 1989.

Uthus EO, Nielsen FH. The effect of vanadium, iodine and their interaction on thyroid status indices. In: *6th International Trace Element Symposium, Vol 1: Molybdenum, Vanadium.* M Anke, W Baumann, H Braunlich, Chr Bruckner, B Groppel, M Grun (eds). Jena, DDR: Karl-Marx-Universitat, Leipzig and Friedrich-Schiller-Universitat, pp 44-49, 1989.

Nielsen FH. Review of book. "Mineral Homeostasis in the Elderly, Current Topics in Nutrition and Disease, Vol 21." Edited by CW Bales. *J Nutr* 119: 1540, 1989.

Nielsen FH. Effects of sulfur amino acids and genetic makeup on the signs of copper deficiency in rats. *J Trace Elem Exp Med* 2: 225-238, 1989.

Nielsen FH, Zimmerman TJ, Shuler TR, Brossart B, Uthus EO. Evidence for a cooperative metabolic relationship between nickel and vitamin B-12 in rats. *J Trace Elem Exp Med* 2: 21-29, 1989.

Berner YN, Shuler TR, Nielsen FH, Flombaum C, Farkouh SA, Shike M. Selected ultratrace elements in total parenteral nutrition solutions. *Am J Clin Nutr* 50: 1079-1083, 1989.

Nielsen FH. The ultratrace elements: Arsenic, boron, chromium, nickel, selenium and silicon. In: *Nutritional Status Assessment of the Individual.* GE Livingston (ed). Trumbull, CT: Food and Nutrition Press, pp 401-415, 1989.

Uthus EO, Nielsen FH. Effects of dietary arsenic, choline and their interaction on arsenic deprivation signs and plasma carnitine in rats. *Proc ND Acad Sci* 43: 87, 1989.

Shuler TR, Nielsen FH. Effects of copper, sulfur amino acids, sex and their interaction on the trace element content of liver and kidney in rats. *Proc ND Acad Sci* 43: 82, 1989.

Poellot RA, Uthus EO, Nielsen FH. Studies on the relationship between nickel and vitamin B-12 in the rat. *Proc ND Acad Sci* 43: 70, 1989.

1988

Shuler TR, Nielsen FH. Boron and methionine status of the rat affects the plasma and bone mineral response to high dietary aluminum. In: *Trace Elements in Man and Animals-6*. LS Hurley, CL Keen, B Lönnerdal, RB Rucker (eds). New York: Plenum Press, pp 581-582, 1988.

Nielsen FH, Mullen LM, Gallagher SK, Hunt JR, Hunt CD, Johnson LK. Effects of dietary boron, aluminum and magnesium on serum alkaline phosphatase, calcium and phosphorus, and plasma cholesterol in postmenopausal women. In: *Trace Elements in Man and Animals-6*. LS Hurley, CL Keen, B Lönnerdal, RB Rucker (eds). New York: Plenum Press, pp 187-188, 1988.

Nielsen FH. Nutritional significance of the ultratrace elements. *Nutr Rev* 46: 337-341, 1988.

Nielsen FH, Shuler TR, Zimmerman TJ, Uthus EO. Dietary magnesium, manganese and boron affect the response of rats to high dietary aluminum. *Magnesium* 7: 133-147, 1988.

Nielsen FH, Shuler TR, Zimmerman TJ, Uthus EO. Magnesium and methionine deprivation affect the response of rats to boron deprivation. *Biol Trace Elem Res* 17: 91-107, 1988.

Nielsen FH. Sulfur amino acid nutriture affects the signs of copper deficiency in the rat. *J Trace Elem Exp Med* 1: 157-166, 1988.

Uthus EO, Nielsen FH. Effects in rats of iron on lead deprivation. *Biol Trace Elem Res* 16: 155-163, 1988.

Greger JL, Krashoc CL, Nielsen FH, Mullen LM. Aluminum metabolism in postmenopausal women. *J Trace Elem Exp Med* 1: 81-88, 1988.

Nielsen FH, Zimmerman TJ, Shuler TR. Dietary potassium affects the signs of boron and magnesium deficiency in the rat. *Proc ND Acad Sci* 42: 61, 1988.

Shuler TR, Nielsen FH. The effect of boron, magnesium, potassium and their interaction on some major mineral elements in liver, kidney and bone. *Proc ND Acad Sci* 42: 59, 1988.

Nielsen FH. Boron - An overlooked element of potential nutritional importance. *Nutr Today* 23: 4-7, 1988.

Nielsen FH. The ultratrace elements. In: *Trace Minerals in Foods*. KT Smith (ed). New York: Marcel Dekker, pp 357-428, 1988.

Nielsen FH. Ultratrace minerals. In: *Modern Nutrition in Health and Disease, 7th ed*. ME Shils, VR Young (eds). Philadelphia, PA: Lea & Febiger, pp 278-291, 1988.

Nielsen FH. Possible future implications of ultratrace elements in human health and disease. In: *Current Topics in Nutrition and Disease: Essential and Toxic Trace Elements in Human Health and Disease, Vol 18*. AS Prasad (ed). New York: Alan R. Liss, pp 277-292, 1988.

1987

Nielsen FH, Hunt CD, Mullen LM, Hunt JR. Effect of dietary boron on mineral, estrogen, and testosterone metabolism in postmenopausal women. *FASEB J* 1: 394-397, 1987.

Nielsen FH. Nutrient Chart No. 7: Nickel. *Dialysis & Transplantation* 16: 203, 1987.

Nielsen FH, Hunt CD, Mullen LM, Hunt JR. Dietary boron affects calcium, phosphorus, and magnesium metabolism of post-menopausal women fed low or adequate magnesium. *Proc ND Acad Sci* 41: 48, 1987.

Shuler TR, Nielsen FH. Effect of boron, calcium, and magnesium and their interaction on the mineral content of kidney and liver from marginally methionine deficient rats. *Proc ND Acad Sci* 41: 49, 1987.

Uthus EO, Nielsen FH. Effects of dietary taurine and arsenic on plasma and liver mineral content in the spontaneously hypertensive rat. *Proc ND Acad Sci* 41: 54, 1987.

Brossart B, Zimmerman TJ, Nielsen FH. Interactions between nickel and vitamin B-12 in the methyl-depleted rat: Effect on growth and blood indices. *Proc ND Acad Sci* 41: 87, 1987.

Nielsen FH. Nickel. In: *Trace Elements in Human and Animal Nutrition, Vol 1, 5th ed.* W Mertz (ed). San Diego: Academic Press, pp 245-273, 1987.

Sinha RK, Nielsen FH, Zimmerman TJ. Effect of dietary Fe on liver Fe, Cu, Zn and Mn in growing rats. *J Inst Chem* (India) 59: 135-136, 1987.

Nielsen FH. Vanadium. In: *Trace Elements in Human and Animal Nutrition, Vol 1, 5th ed.* W Mertz (ed). San Diego: Academic Press, pp 275-300, 1987.

Uthus EO, Nielsen FH. Methyl depletion affects the response of rats to arsenic deprivation. *Nutr Res* 7: 1061-1072, 1987.

Uthus EO, Nielsen FH. The essential role of arsenic in the nutrition of animals. Preprints of Papers, *Amer Chem Soc* 27: 120-122, 1987.

Nutrition, Physiology, and Behavior

Mission

The Nutrition, Physiology, and Behavior Management Unit plans, implements, and interprets research that is designed to produce new knowledge about human nutrient requirements with an emphasis on trace elements. The research will identify human needs necessary for achievement of optimal physiologic and psychological function and performance based on genetic potentials throughout the life cycle, and provide information for decisions concerning the provision of a healthful food supply to the population of the United States.

Animal models are used to provide information useful in planning studies with human volunteers, including safety, new analytical methods, and demonstration of the usefulness of measuring previously ignored characteristics and responses. Information provided by the animal models will be used to elucidate the metabolism of the mineral elements, including the effects of mineral element deficiencies and excesses on other nutrients and to identify functional changes and/or adaptive mechanisms affecting responses to mineral nutrients. Research on animals provides the background for human studies by investigating hypotheses in ways that would be inappropriate for humans.

Human volunteers are studied under controlled conditions of a metabolic research ward or as free-living individuals to determine the effects of graded trace element intakes on physiologic and psychological function and performance in response to static and dynamic stressors and challenges. The responses are evaluated and compared with standard and new biochemical indices of trace element status to identify impairments in function and performance. This information is necessary to determine previously unrecognized metabolic roles of essential and other trace elements.

Research Leader

Henry C. Lukaski, Ph.D.
Supervisory Research Physiologist
(701) 795-8429

Mary Rydell
Secretary
(701) 795-8464

Applied Physiology Laboratory

Mission

To determine the influence of alterations in trace element nutriture on static and dynamic physiologic, metabolic, and endocrine functions during acute and chronic exposure to stressors such as maximal and submaximal work and altered environmental conditions. To assess the effect of chronic high energy expenditure, with and without weight loss, on human trace element requirements. To develop and validate functional tests of nutritional assessment, and new approaches to assess human body composition. To determine the interactions among nutrition, body structure and function.

Lead Scientist

Henry C. Lukaski, Ph.D.
Supervisory Research Physiologist
(701) 795-8429

Staff

Clinton B. Hall, M.S.
Biologist
(701) 795-8495

William A. Siders, M.S.
Biologist
(701) 795-8430

Kim G. Michelsen, B.S.
Biological Laboratory Technician
(701) 795-8357

Mary E. Sleeper
Biological Laboratory Technician
(701) 795-8357

Recent Research Accomplishments

Developed and validated the tetrapolar bioelectrical impedance method for assessing human body composition. Models for predicting densitometrically determined fat-free mass based upon conductance measurements of the body were developed and cross-validated in adults. The error of estimating fat-free mass was within the limits of the reference method of assessing body composition. The predictive accuracy was less than that found by standard anthropometric procedures. Other studies resulted in the development and validation of models using impedance measurements to estimate total body water and extracellular water in healthy adults. These relationships were subsequently used to assess fluid changes in surgical patients.

Provided first evidence that copper status affects human blood pressure. Significant increases in systolic and diastolic blood pressure responses during five minutes of isometric hand-grip exercise were exhibited by eight women consuming diets low in copper (0.65 mg/d) and supplemented with ascorbic acid (1.5 g/d). Resting blood pressures were not affected by low copper intake. These findings indicate a functional alteration in human blood pressure regulation during mild copper depletion.

Identified a unique biochemical adaptation associated with aerobic physical training. Significant increases in a copper- and zinc-containing enzyme, superoxide dismutase, responsible for destruction of oxygen free-radicals were observed in male and female collegiate swimmers after a competitive season. No changes were found in age-matched, non-training control subjects. The observed changes in the

swimmers indicate a homeostatic response in copper metabolism to protect skeletal muscle from oxidative damage.

Developed and implemented a program for the prescription of aerobic exercise to maintain body composition and physical fitness of human volunteers residing on a metabolic unit. Use of this program facilitates control of energy expenditure so that biochemical and physiological changes can be attributed with confidence to altered micronutrient intake.

Demonstrated that iron deficiency without overt anemia in humans is associated with impairments in energy metabolism. A reduced thermogenic response during acute cold exposure and a blunted rate of oxygen utilization during progressive exercise to exhaustion were observed in 12 women who were made iron-deficient by a combination of reduced iron intake, phlebotomy, and menstruation. It is noteworthy that the apparent inability to produce heat in the cold and reduced rate of oxygen uptake during work were associated with an increase in anaerobic metabolism. These data indicate that iron-dependent factors other than oxygen-carrying capacity can influence body metabolism.

Identified that zinc deficiency impairs thyroid hormone status in animals. Significant decreases in circulating thyroid hormones are characteristic of severely zinc-deficient rats, particularly when the animals are acutely exposed to cold. In moderately zinc-deficient rats, there is a reduction in processing of thyrotropin-releasing hormone precursor peptides in the brain that may be explained by reduced activity of two zinc-dependent enzymes. These findings indicate a new biological role of zinc in thyroid hormone metabolism.

Publications

Henry C. Lukaski has collaborated on six additional publications shown in the reference lists of Analytical Biochemistry Laboratory; Dietary Interactions and Required Nutrient Intakes Laboratory; Trace Elements and Cardiovascular Health Laboratory; Absorption and Homeostasis of Trace Elements Laboratory; and Cardiovascular Physiology Laboratory.

1991/1992

Lukaski HC, Hall CB. Effects of zinc deficiency and starvation on thermogenesis of rats in the cold. *Horm Metab Res* (In press).

Lukaski HC. Bioelectrical impedance analysis: clinical applications. *Nutrition* (In press).

Lukaski HC. Critique of the military's approach to body composition assessment and evaluation. In: *Body Composition Standards and Military Performance*. Washington, DC: National Academy of Sciences (In press).

Lukaski HC, Johnson PE. Dietary fatty acids and minerals. In: *Fatty Acids in Foods and Their Health Implications*. CK Chow (ed). New York: Marcel Dekker (In press).

Tripp M, Megiud MM, Lukaski HC, Rosenburg J, Parker F. Rapid bedside method to assess postoperative fluid balance using bioelectrical impedance analysis. *Surgery* (In press).

Lukaski HC, Siders WA, Hall CB. Validity of body mass index corrected for sex and age to predict human body composition in adults. *Proc ND Acad Sci* 46: 50, 1992.

Siders WA, Lukaski HC. Body composition and collegiate volleyball performance. *Proc ND Acad Sci* 46: 51, 1992.

Smith SM, Lukaski HC. Estrous cycle and cold stress in iron-deficient rats. *J Nutr Biochem* 3: 23-30, 1992.

Lukaski HC. Body composition assessment using impedance methods. In: *Obesity*. P Bjorntorp, BN Brodoff (eds). Philadelphia: JB Lippincott Co, pp 67-79, 1992.

Swantek PM, Crenshaw JD, Marchello MJ, Lukaski HC. Bioelectrical impedance: A nondestructive method to determine fat-free mass of live market swine and pork carcasses. *J Anim Sci* 70: 169-177, 1992.

Lukaski HC. Electrical impedance offers promise of reliable body fat measures. *Obesity and Health* 5: 47, 1991.

Lukaski HC, Hall CB, Siders WA. Altered metabolic response of iron-deficient women during graded, maximal exercise. *Eur J Appl Physiol* 63: 140-145, 1991.

Lukaski HC. Laboratory assessment of human body composition. *Obesity and Health* 5: 63, 1991.

Pekary AE, Lukaski HC, Mena I, Hershman JM. Processing of TRH precursor peptides in rat brain and pituitary is zinc dependent. *Peptides* 12: 1025-1032, 1991.

Bolonchuk WW, Lukaski HC Siders WA. The structural, functional, and nutritional adaptation of college basketball players over a season. *J Sports Med Phys Fitness* 31: 165-172, 1991.

Lukaski HC. Assessment of body composition using tetrapolar bioelectrical impedance analysis. In: *New Techniques in Nutritional Research*. RG Whitehead, A Prentice (eds). San Diego: Academic Press, pp 303-315, 1991.

Lukaski HC. Bioimpedance. In: *Encyclopedia of Human Biology, Vol 1*. R Dulbecco (ed). San Diego: Academic Press, pp 667-674, 1991.

Lukaski HC. Bioelectrical impedance: basic principles and studies in normal controls. *Proc Fifteenth Clin Cong Am Soc Parenteral Enteral Nutr. Postgrad Course No. 12: Applications of New Res in Nutr and Body Comp*, pp 28-31, 1991.

Siders WA, Lukaski HC, Bolonchuk WW, Hall CB. The frequency distribution of somatotype in a sample. *Proc ND Acad Sci* 45: 28, 1991.

1990

Lukaski HC, Hall CB, Nielsen FH. Thermogenesis and thermoregulatory function of iron-deficient women without anemia. *Aviat Space Environ Med* 61: 913-920, 1990.

Lukaski HC, Hoverson BS, Gallagher SK, Bolonchuk WW. Physical training and copper, iron, and zinc status of swimmers. *Am J Clin Nutr* 51: 1093-1099, 1990.

Brechue WF, Stager JM, Lukaski HC. Body water and electrolyte responses to acetazolamide in humans. *J Appl Physiol* 69: 1397-1401, 1990.

Lukaski HC, Bolonchuk WW, Siders WA, Hall CB. Body composition assessment of athletes using bioelectrical impedance measurements. *J Sports Med Phys Fitness* 30: 434-440, 1990.

Lukaski HC. Applications of bioelectrical impedance analysis: A critical review. In: *In Vivo Body Composition Studies--Recent Advances*. S Yasumura, JE Harrison, KG McNeill, AD Woodhead, FA Dilmanian (eds). New York: Plenum Publishing Corp, pp 365-374, 1990.

Lykken G, Ong W, Patrick D, Wielopolski L. Rn-222 and Rn-222 progeny in the human body: Effect on *in vivo* K-40 measurements. In: *In Vivo Body Composition Studies - Recent Advances*. S Yasumura, JE Harrison, KG McNeill, AD Woodhead, FA Dilmanian (eds). New York: Plenum Press, pp 361-363, 1990.

Bolonchuk WW, Lukaski HC, Siders WA, Hall CB. The body composition of dominant and modified somatotypes. In: *Exercise Physiology: Current and Select Research, Vol 4*. CO Dotson, JH Humphrey (eds). New York: AMS Press, pp 145-157, 1990.

Lukaski HC. Physical training and trace element status. *Proc ND Acad Sci* 44: 46, 1990.

Lukaski HC. Assessment of body composition using bioelectrical impedance analysis. *Proc 14th Clin Cong Am Soc Parent Enter Nutr*, pp 135-137, 1990.

Bolonchuk WW. Body composition and performance. *Proc ND Acad Sci* 44: 48, 1990.

Bolonchuk WW, Lukaski HC, Siders WA. The effect on the analysis of grouping data by somatotype component or by somatotype dominance. *Proc ND Acad Sci* 44: 53, 1990.

Hall CB, Perreault C, Lukaski HC. A low copper diet influences thermoregulation of the rat. *Proc ND Acad Sci* 44: 60, 1990.

Siders WA, Lukaski HC, Bolonchuk WW, Hall CB. Body composition and swimming performance: A two-year study. *Proc ND Acad Sci* 44: 88, 1990.

1989

Lukaski HC, Hoverson BS, Milne DB, Bolonchuk WW. Copper, zinc, and iron status of female swimmers. *Nutr Res* 9: 493-502, 1989.

Lukaski HC, Bolonchuk WW, Klevay LM. Comparison of metabolic responses and oxygen cost during maximal exercise using three treadmill protocols. *J Sports Med* 29: 223-229, 1989.

Lukaski HC, Bolonchuk WW. Maintenance of aerobic capacity and body composition of volunteers residing on a metabolic research unit. *J Sports Med* 29: 273-278, 1989.

Hall CB, Lukaski HC, Marchello MJ. Estimation of rat body composition using tetrapolar bioelectrical impedance analysis. *Nutr Rep Int* 39: 627-633, 1989.

Bolonchuk WW, Hall CB, Lukaski HC, Siders WA. Relationship between body composition and the components of somatotype. *Am J Hum Biol* 1: 239-248, 1989.

Lukaski HC. Use of bioelectrical impedance analysis to assess human body composition: A review. In: *Nutritional Status Assessment of the Individual*. GE Livingston (ed). Trumbull, CT: Food and Nutrition Press, pp 189-204, 1989.

Lukaski HC. Effects of exercise training on human copper and zinc nutriture. In: *Copper Bioavailability and Metabolism*. C Kies (ed). New York: Plenum, pp 163-170, 1989.

Lukaski HC. Methods for the assessment of human body composition. *Proc ND Acad Sci* 43: 8, 1989.

Bolonchuk WW, Lukaski HC, Siders WA. Assessment of physique and its relationship to physiological function. *Proc ND Acad Sci* 43: 10, 1989.

Hall CB, Lukaski HC, Perreault CG. Effects of zinc deficiency on temperature regulation by rats in the cold. *Proc ND Acad Sci* 43: 48, 1989.

Lykken GI, Ong WS. Evidence of exhalation of stored environmental Rn determined by whole-body counting. *Health Physics* 57: 161-162, 1989 (Note).

Siders WA, Lukaski HC, Bolonchuk WW, Hall CB. Somatotype and sex bias in the use of body mass index to classify overweight and obesity. *Proc ND Acad Sci* 43: 83, 1989.

1988

Lukaski HC, Klevay LM, Milne DB. Effects of dietary copper on human autonomic cardiovascular function. *Eur J Appl Physiol* 58: 74-80, 1988.

Lukaski HC, Bolonchuk WW. Estimation of body fluid volumes using tetrapolar bioelectrical impedance measurements. *Aviat Space Environ Med* 59: 1163-1169, 1988.

Meguid MM, Campos ACL, Lukaski HC, Kiell C. A new single cell in-vitro model to determine volume and sodium concentration changes by bioelectrical impedance analysis. *Nutrition* 4: 363-366, 1988.

Lukaski HC, Hoverson BS, Bolonchuk WW. Trace element nutriture of female competitive swimmers. *Proc ND Acad Sci* 42: 58, 1988.

Hoesley T, Lukaski HC. A high pressure liquid chromatography method to measure bromine in plasma. *Proc ND Acad Sci* 42: 36, 1988.

Lykken GI, Ong WC, Patrick DP. Radon-222 and radon-222 daughter uptake in the body: Effects of a mask and an electronic air filter on bismuth-214 counts. *Proc ND Acad Sci* 42: 38, 1988.

Bolonchuk WW, Siders WA, Lukaski HC. Structural and functional correlates of exercise and training. *Proc ND Acad Sci* 42: 45, 1988.

Siders WA, Lukaski HC, Hall CB, Bolonchuk WW. Validity of relative weight indices for predicting percent body fat. *Proc ND Acad Sci* 42: 46, 1988.

Hall CB, Lukaski HC, Marchello MJ. Determination of rat body composition using bioelectrical impedance analysis. *Proc ND Acad Sci* 42: 47, 1988.

Lukaski HC. Body composition methods (Reply). *Am J Clin Nutr* 47: 1088, 1988.

1987

Lukaski HC. Potential uses of bioelectrical conductance methods. *Nutr Int* 3: 66, 1987.

Lukaski HC. Methods for the assessment of human body composition: Traditional and new. *Am J Clin Nutr* 46: 537-556, 1987.

Lykken GI, Speaker KK, MacKichian AK. Estimation of total body potassium in the presence of interfering radioisotopes. In: *In Vivo Body Composition Studies*. KJ Ellis, S Yasumura, WD Morgan (eds). London, England: The Institute of Physical Sciences in Medicine, pp 114-117, 1987.

Lukaski HC, Bolonchuk WW. Theory and validation of the tetrapolar bioelectrical impedance method to assess human body composition. In: *Proceedings of the International Symposium on In Vivo Body Composition Studies*. KJ Ellis, S Yasumura, WD Morgan (eds). London: Institute of Physical Sciences in Medicine, pp 410-414, 1987.

Khaled MA, Lukaski HC, Watkins CL. Determination of total body water by deuterium NMR. *Am J Clin Nutr* 45: 1-6, 1987.

Bolonchuk WW, Lukaski HC. Changes in somatotype and body composition of college football players over a season. *J Sports Med Phys Fitness* 27: 247-252, 1987.

Bolonchuk WW, Lukaski HC, Hall CB, Siders WA. Body composition of dominant somatotype groups. *Proc ND Acad Sci* 41: 45, 1987.

Lukaski HC. Body composition methodology: An introduction. In: *AIN Symposium Proceedings. Nutrition '87*. OA Levander (ed). Bethesda, MD: American Institute of Nutrition, pp 76-77, 1987.

Lukaski HC. Bioelectrical impedance analysis. In: *AIN Symposium Proceedings. Nutrition '87*. OA Levander (ed). Bethesda, MD: American Institute of Nutrition, pp 78-81, 1987.

Cardiovascular Physiology Laboratory

Mission

To determine the functional changes in heart, circulation, and related systems caused by trace element deficiencies and, by use of physiological, pharmacological, and biochemical techniques, to ascertain the mechanism of those changes.

Lead Scientist

Jack T. Saari, Ph.D.
Research Physiologist
(701) 795-8499

Staff

Corrie B. Allen, Ph.D.
Research Physiologist
Postdoctoral Research Associate
(701) 795-8498

Jackie Keith
Biological Laboratory Technician
(701) 795-8498

Gwen M. Schelkoph
Chemist
(701) 795-8498

Recent Research Accomplishments

Demonstrated that the administration of antioxidants to laboratory animals, either by feeding or injection, can inhibit the development of cardiac enlargement, cardiac edema, and anemia caused by dietary copper deficiency.

Collaborated in a study which showed that ethane production, an indicator of lipid peroxidation, is enhanced when laboratory rats are fed a diet deficient in copper.

Demonstrated, in a collaborative study, that copper deficiency in rats enhances lung damage caused by breathing oxygen under high pressure. This further suggests that copper-deficient animals are vulnerable to oxidative stress.

Collaborated in research showing that microvascular function in rats is altered in copper deficiency. Specifically, copper deficiency enhanced the increase in microvascular permeability caused by release of histamine and inhibited adhesion of platelets to microvessel walls. This suggests that inflammation is enhanced and hemostatic (clotting) function is reduced in copper deficiency. Further studies of microvascular function showed that, though high blood cholesterol depressed copper status, the effects on inflammation and clotting were the opposite from those of copper deficiency.

Found that the aortas of copper-deficient rats are less capable of relaxing in response to agents which require an intact blood vessel endothelium for their action. Demonstrated, in a collaborative study, that endothelium-dependent relaxation is also disrupted in the microcirculation of copper-deficient rats. This suggests a mechanism for the development of high blood pressure in copper deficiency.

Co-produced a series of studies illustrating that copper deficiency causes alteration of renal composition, enzyme activity, clearance function, and body water retention. Further, renal damage by cis-platinum, an anti-tumor agent and nephrotoxin, is exaggerated in copper deficiency. Obtained evidence that cis-platinum acts by producing O_2-derived free radicals, which suggests that copper deficiency potentiates cis-platinum damage by reducing antioxidant defenses.

Co-produced a study which demonstrated that mitochondrial respiration is impaired in hearts of copper-deficient rats.

Publications

Jack T. Saari has collaborated on four additional publications shown in the reference lists of Cell Membrane Biochemistry Laboratory and Peptide Hormone Metabolism and Cell Culture Laboratories.

1991/1992

Saari JT. Dietary copper deficiency and endothelium-dependent relaxation of rat aorta. *Proc Soc Exp Biol Med* (In press).

Schuschke DA, Reed MWR, Saari JT, Miller FN. Differential effects of copper deficiency on vasodilation in the rat cremaster muscle microcirculation. *J Nutr* (In press).

Bode AM, Miller LA, Faber J, Saari JT. Mitochondrial respiration in heart, liver and kidney of copper-deficient rats. *J Nutr Biochem* (In press).

Saari JT, Medeiros DM. Effect of dimethyl sulfoxide on enlarged hearts of copper-deficient rats. *Biol Tr Elem Res* 31: 249-263, 1991.

1990

Saari JT, Schuschke DA, Ackermann DM, Miller FN. Effects of cholesterol feeding and copper deficiency on inflammation and thrombosis. *Proc ND Acad Sci* 44: 82, 1990.

Schelkoph GM, Saari JT. Detection of sulfite and sulfate in serum and urine using ion chromatography. *Proc ND Acad Sci* 44: 84, 1990.

Saari JT, Reeves PG, Noordewier B, Hall CB, Lukaski HC. Cardiovascular but not renal effects of copper deficiency are inhibited by dimethyl sulfoxide. *Nutr Res* 10: 467-477, 1990.

Schuschke DA, Saari JT, Ackermann DM, Miller FN. Progressive microcirculatory changes caused by hypercholesterolemia in rats. *Am J Physiol* 258: H1464-H1469, 1990.

Saari JT, Dickerson FD, Habib MP. Ethane production in copper-deficient rats. *Proc Soc Exp Biol Med* 195: 30-33, 1990.

1989

Schuschke DA, Saari JT. Histamine-mediated vasoconstriction and cAMP levels in coronary arteries of the isolated rabbit heart. *Pharmacology* 38: 23-33, 1989.

Saari JT. Chronic treatment with dimethyl sulfoxide protects against cardiovascular defects of copper deficiency. *Proc Soc Exp Biol Med* 190: 121-124, 1989.

Saari JT, Johnson WT. Inhibition of cardiovascular effects of copper deficiency with antioxidants. *Proc ND Acad Sci* 43: 80, 1989.

Schuschke DA, Saari JT, Ackermann DM, Miller FN. Microvascular responses in copper-deficient rats. *Am J Physiol* 257: H1607-H1612, 1989.

1988

Saari JT, Klevay LM. Effect of dietary copper deficiency on vagal innervation of the heart. *Proc ND Acad Sci* 42: 63, 1988.

1987

Barman SA, Olson MD, Saari JT. Effect of histamine on cardiac sarcolemmal calcium binding as indicated by use of ionic lanthanum. *Cardiovascular Res* 21: 569-575, 1987.

Barman SA, Olson MD, Saari JT. Histamine-induced alteration of calcium binding to microvascular endothelium as indicated by use of ionic lanthanum. *Cardiovascular Res* 21: 576-581, 1987.

Trace Element Nutrition, Neuropsychological Function, and Behavior Research Laboratory

Mission

To apply psychological and neurophysiological principles and methods to the understanding of adult human behavior as influenced by nutrient intake and status, and to determine the dietary requirements for trace elements to achieve and maintain optimal cognitive performance and emotional adjustment in humans. To determine potential mediating factors in the nutrition-behavior relationship, including endogenous and exogenous stressors. To determine the effects of trace element nutrition on electrophysiology indexing cortical activity and autonomic activity to provide insight into the mechanisms for nutritional effects on psychological processes relevant to performance and adjustment. To develop methods of assessing behavior and neuropsychological responses in healthy adults which are sensitive to nutritional effects arising from marginal deficiencies and subclinical states.

Lead Scientist

James G. Penland, Ph.D.
Research Psychologist
(701) 795-8471

Staff

Gloria J. Krank, B.S.
Psychologist
(701) 795-8417

Jay G. Dahlgren, B.S.
Psychology Technician
(701) 795-8427

Tonya C. Murphy, B.S.
Biological Laboratory Technician
(701) 795-8458

Rebecca J. Stadstad
Psychology Technician
(701) 795-8385

Recent Research Accomplishments

Produced the first evidence that dietary boron may be important for brain function in animals. Electrocorticographic (ECoG) data were collected from 100-day-old male and female rats fed either 0.12 or 2.71 μg/g boron for approximately 10 weeks. Low dietary boron decreased ECoG activity in both left and right hemispheres, particularly in the higher frequencies, and increased the proportion of lower frequency activity while decreasing the proportion of higher frequency activity.

Produced the first evidence that dietary boron may be important for brain function in healthy, older adults. In one study, electroencephalographic (EEG) data were collected from 13 healthy postmenopausal women fed either 0.23 or 3.23 mg/d boron as part of a 6-month metabolic unit study. Low dietary boron increased low-frequency EEG activity in parietal and left occipital regions of the head and increased the proportion of lower to higher frequency activity, primarily in the frontal regions. In a second study, EEG data were collected from 10 healthy women (9 postmenopausal) and 5 healthy men older than 45 years fed either 0.23 or 3.23 mg/d boron as part of a 4-month free-living community study. Low dietary boron decreased EEG activity in the higher frequencies in the anterior regions of the head and in the lower frequencies in the posterior regions and increased the proportion of lower frequency

activity while decreasing the proportion of higher frequency activity. In addition, low boron resulted in a greater left-minus-right hemisphere asymmetry in EEG activity.

Produced the first evidence that dietary boron may be important for sensory-motor function and cognitive performance. Data collected during the second study described above showed that the lower boron intake resulted in impaired performance on tapping, pursuit, search, counting, and encoding tasks.

Found that dietary calcium and manganese intakes were related to menstrual symptomatology in 10 healthy women with normal menstrual cycles as part of a six-month, live-in metabolic study. Diets were fed in a Latin-square, double-blind manner for 39 days each. In contrast to when they were fed 1,336 mg calcium/2,000 kcal/day, women fed 587 mg calcium reported increased negative mood, more behavioral problems, and poorer concentration throughout the menstrual cycle. Low calcium also resulted in reports of greater pain during the menstrual phase and increased water retention during the premenstrual phase. An interaction between dietary manganese (1.0 versus 5.6 mg/2,000 kcal/day) and calcium showed that, despite the presence of high dietary calcium, low manganese intake resulted in increased negative mood during the premenstrual phase.

Determined dietary zinc effects on cognitive processes and sensory-motor skills in 14 healthy men as part of a 7-month, live-in metabolic study. Subjects were fed 1, 2, 3, or 4 mg zinc/2,500 kcal/day during each of four 35-day dietary periods fed in a random, double-blind manner. When contrasted with performance during a 35-day control period providing 10 mg zinc, response time and errors on tasks measuring attention, perception, memory, and spatial and sensory-motor skills showed poorer performance with lower Zn intakes. However, there were few differences among the low zinc periods to support a "dose" effect.

Found that responses to a standardized self-report measure of mood states were related to dietary intakes and blood concentrations of aluminum, calcium, copper, iron, magnesium, manganese, and zinc in healthy adult women participating in six independent, live-in studies of trace element nutrition. Dietary effects on mood states were evident in all six studies, with higher intakes of aluminum, copper, and iron, and lower intakes of magnesium and zinc associated with more positive mood states. Correlations between mood states and concentrations of copper, iron, magnesium, and zinc in the blood were numerous, but were often inconsistent when data from different studies were compared. Results were interpreted as providing only weak support for a trace element-mood relationship.

Determined sleep patterns in healthy, young-adult women participating in several independent, live-in studies of trace element nutrition and related to dietary intakes. Compared to when they consumed >2 mg/day copper, 11 women consuming <1 mg/day copper reported earlier bedtimes, longer latency to sleep, longer total sleep time, and feeling less rested upon awakening. In contrast to when they were fed >15 mg/day iron, 13 women fed <5 mg/day iron reported earlier bedtimes, more nighttime awakenings, and longer total sleep time. Results were interpreted as providing moderate support for a trace element-sleep behavior relationship.

Produced the first evidence of a relationship between dietary copper and brain function in animals. ECoG data were collected from male rats fed 0.7, 1.4, or 2.7 μg/g copper for 100 days following weaning. Rats with the lowest copper intake showed decreased low-frequency amplitudes, increased middle- and higher-frequency amplitudes, and increased right-minus-left hemisphere asymmetries. Results suggest that copper deficiency may shift brain arousal and increase laterality of activity.

Developed a computer software package to automate the administration of standardized psychological tasks designed to assess a variety of cognitive processes (for example, sensation, perception, attention, learning, memory, decision making), and spatial and sensory-motor skills in healthy adults. This system has been used in several studies of nutrition and cognition at both the Grand Forks and Western Human Nutrition Research Centers. Also developed and standardized several paper-and-pencil measures

designed to assess mood states, stress, psychosocial behavior, daily activity levels, and sleep behavior of adults participating in metabolic unit and free-living studies of nutrition.

Found a relationship between several measures of iron status, cognitive performance, and EEG parameters of healthy, older (>55 years) adults. Short-term memory for numerical sequences was poorer in individuals with low iron status. Iron status was related to higher amplitudes in the lower EEG frequencies in the posterior regions of the brain, but to lower amplitudes in the higher frequencies recorded from anterior regions.

Publications

1991/1992

Penland JG, Johnson PE. Dietary calcium and manganese effects on menstrual cycle symptomatology. *Am J Obstet Gynecol* (In press).

Penland JG. Effects of dietary boron on the brain electrophysiology of healthy adults. *Am J Clin Nutr* (In press).

Penland JG, Klevay LM. Caloric restriction and increased exercise in mildly obese women. I. Effects on menstrual symptomatology and plasma monoamine oxidase activity. *Proc ND Acad Sci* 46: 52, 1992.

Krank GJ, Penland JG, Klevay LM. Caloric restriction and increased exercise in mildly obese women. II. Effects on sleep behavior and serotonin. *Proc ND Acad Sci* 46: 53, 1992.

1990

Tucker DM, Penland JG, Sandstead HH, Milne DB, Heck DG, Klevay LM. Nutrition status and brain function in aging. *Am J Clin Nutr* 52: 93-102, 1990.

Penland JG. Dietary boron affects brain function in mature Long-Evans rats. *Proc ND Acad Sci* 44: 78, 1990.

1989

Penland JG Sawler BG, Klevay LM. Brain electrophysiology in adult rats fed copper deficient diets. *J Trace Elem Exp Med* 2: 239-256, 1989.

Ong HS, Lykken GI. Environmental radon uptake in humans: An enigma? *Proc ND Acad Sci* 43: 67, 1989.

Penland JG. Relationship between essential trace element nutrition and self-reported mood states. *Proc ND Acad Sci* 43: 68, 1989.

1987

Eberhardt MJ, Halas ES. Developmental delays in offspring of rats undernourished or zinc deprived during lactation. *Physiol Behav* 41: 309-314, 1987.

Halas ES, Eberhardt MJ. A behavioral review of trace element deficiencies in animals and humans. *Nutr Behav* 3: 257-271, 1987.

Health Care and Community Studies

Mission

To work with principal investigators to design protocols appropriate for human studies and to ensure approved studies are implemented as planned. To ensure suitable participants are available for nutritional research on humans. To provide and/or monitor health care for research participants.

Donna Neese, R.N., B.S.N., M.S.
Nurse Consultant
(701) 795-8380

Emily Nielsen, R.N., B.S.N.
Nurse Specialist
(701) 795-8401

Units Supervised by University of North Dakota Employees

The Federal staff of the Grand Forks Human Nutrition Research Center is supported by services from approximately 120 persons supplied through a Research Support Agreement with the University of North Dakota. The services include automatic data processing, janitorial, maintenance, routine laboratory, animal care, dishwashing, clinical laboratory, nursing, kitchen, dietary, recruiting, clerk-typist, and information processing.

Supervisor	Service/Unit	Federal Monitor
Joan Flynn	Information Processing Equipment Operator	Diane Nath Phyllis Groven
Cody Jensen	Clerk/Typist	Diane Nath
Sandra Gallagher	Clinical Laboratory Routine Laboratory (Student Helpers) Glassware	David Milne Federal Support Staff Forrest Nielsen
LuAnn Johnson	Data Processing	Forrest Nielsen
Bonita Hoverson	Dietary-Food Services Metabolic Ward Studies	Janet Hunt
Lori Matthys	Dietary-Nutrient Data Base Community Studies	Janet Hunt
Betty Vetter	Metabolic Unit	Donna Neese
Bonnie Thompson	Custodial	Phyllis Groven
Denice Schafer	Vivarium	Eric Uthus
Rodney Bubach	Maintenance	Phyllis Groven
Joan Flynn	Recruiting Overall Business Manager/Supervisor	Donna Neese Forrest Nielsen

☆U.S. GOVERNMENT PRINTING OFFICE: 1992-656-953 60208

NATIONAL AGRICULTURAL LIBRARY
1022323202

NATIONAL AGRICULTURAL LIBRARY
1022323202